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CAFFEINE

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CAFFEINE

Summary

The United States imported in 1970 from The Netherlands and West Germany 1,616,264 pounds of caffeine valued at $2,109,743. In the same year, imports of coffee were 19,727,000 bags of 60 kilos or 132.276 pounds each; tea imports were 137,201,000 pounds; and cacao beans were 625,432,000 pounds (U. S. Department of Commerce reports).

Not only is caffeine a valuable therapeutic agent, but as the chief component of beverages made from the seeds of Coffea arabica and Theobroma cocao, or the leaves of Thea sinensis, it has enjoyed wide use as a stimulant since ancient times. Maté, the popular drink of South America contains caffeine, as do the many cola "soft drinks" made from extracts of the kola nut and found world-wide.

Legendary origins of the discovery of coffee credit an Arabian monastery whose Abbott heard from shepherds of the extraordinary liveliness of goats who ate the berries of the coffee plant, and who, himself, brewed a beverage from the berries. With the exception of a few religious groups, coffee and tea drinking has enjoyed social acceptance almost universally. Some prejudice has existed in the use of caffeine-containing beverages, particularly among children, probably due to the association of the term "stimulant" with alcohol and its abuses. Caffeine, pharmacologically, is a true stimulant of the central nervous system and skeletal muscle, quite unlike alcohol which is essentially a depressant and quite dissimilar in its action. Punnett (2587), chief chemist in 1942 for the Good Housekeeping Bureau in New York City, presented a refutation of the bad reputation of caffeine and the food products containing it. Various methods of brewing coffee and tea, and preparing chocolate products, with the resultant amounts of caffeine and theobromine in various foods, are presented by Punnett. The average cup of tea will contain 60-75 mg of caffeine; coffee varies in caffeine from 68 to 101 mg per cup; and several brands of "cola" beverages contain from 6 to 9 mg per ounce. Cocoa and chocolate drinks are low in caffeine, but the candy bar milk chocolate has about the same amount of caffeine as a cup of tea or coffee.

Loeffler (1978) in 1969 presented a concise monograph on caffeine which has been translated and included in the document section of this monograph. Historically, Loeffler credits to Friedrich Ferdinand Runge the discovery of caffeine in 1820. Since that time, thousands of studies and reports on the effects of caffeine in the human, and even plant and lower animals (e.g. Drosophila and mice), have been published; (the present monograph lists about 5000 references) indicating both beneficial therapeutic and social aspects of the drug, and the possible harmful results of ingesting it. The human reactions have been shown to be highly variable; the amounts of caffeine consumed ranging from one or two cups of coffee (or tea) daily (100-300 mg caffeine) to a dozen or more, exceeding a gram of caffeine daily over a period of years without

apparent ill effects. The numerous references to coffee in a monograph devoted to caffeine are unavoidable. Much of the experimentation involving the effects of caffeine, particularly in human studies, has dealt with coffee - for it has been generally assumed that caffeine is the "active principle" and that we are studying the effects of caffeine when we study the effects of coffee-drinking. Controversy still surrounds the drinking of coffee; an excerpt from a paper by Ralph Holt Cheney (549) in 1934, and a clipping from the Alexandria Gazette, January 29, 1974 will serve to point out the problem:

RELATION OF CAFFEINE AND COFFEE TO HUMAN EFFICIENCY.*

BY RALPH HOLT CHENEY.

Efficiency and diet occupy a more prominent position in the public mind to-day than in all previous history. At the moment, caffeine beverages, especially coffee, are lauded or berated vigorously regarding their value in the diet in relation to human efficiency.

Based upon "whims and guesses," coffee has been praised or condemned for centuries. What is the scientific evidence "pro" and "con?" Historically, we find a prohibition edict by Khaine Beg, Governor of Mecca in 1511, who started a campaign which condemned coffee as an inebriating beverage forbidden by the Koran because the people frequented coffee houses rather than the mosques. Coffee and coffee houses were taxed by European governments as a source of revenue. Later, coffee houses were prohibited by Charles II of England as "Seminaries of Sedition." Coffee houses have served as gathering places for public discussions of governmental affairs. They were the predecessors of the boulevard cafés of Paris and the coffee-house taverns of England. This English prototype appeared in the United States where the coffee houses of Boston and New York harbored the instigators of the Boston Tea Party and revolutionary propaganda.

In spite of six hundred years of agitation associated with coffee, its consumption has increased constantly from an insignificant amount to three billion pounds annually, and its use has spread from the Abyssinian hillsides to world-wide consumption. Mocha coffee from the original home of the plant now supplies less than 3% of the seeds (coffee beans) of this sweet-pulped, cherry-like fruit which was introduced in America in 1717. Its cultivation has changed the economic map of several countries. Brazil has two billion coffee trees, Colombia a quarter billion, and the success or failure of the crop is the chief factor in the economic situation in these countries. Eighty per cent of the total gold value of Salvadorean exports is coffee. Although the plant is foreign to American soil, no better coffee is marketed to-day than the Colombian or Brazilian Santos from the Uplands where it is prepared by the most modern methods.

The United States consumes over one-half of all the coffee exported from the cultivated areas. New York City requirements annually total seventy million pounds, for which we pay thirty million dollars. Space limitation causes me to refer you to a book, "Coffee" (1), published by the New York University Press, for botanical characteristics; and also, for further details of the interesting, romantic history and economics of the plant and its beverage.

Undoubtedly, more scientific experimentation on the subject of caffeine and coffee effects has been conducted during the last twenty-five years than in all previous time. The results of such investigations are the only justifiable bases from which we may make our deductions regarding the physiological effects of the coffee as such, and of its individual ingredients.

Speaking of Your Health

by LESTER L. COLEMAN, M.D.

COFFEE'S ILL EFFECT: PRO AND CON

Can excess coffee drinking cause heart disease?

Mr. T. D. O., Pa.

DEAR Mr. O.:

A considerable amount of interest and confusion exists about this important matter. Widespread publicity was given this when a study was reported in leading British Medical Journal, LANCET. In it, coffee was linked to some cases of coronary heart disease.

Then came a release from the Kaiser-Permanente Center in California which just as positively stated, "There is no independent association between coffee drinking and a subsequent first myocardial infraction (heart attack).

This research team found that those who drank more than six cups of coffee a day were much more likely to smoke a great many cigarettes a day. It was believed by this group that the cigarettes rather than the coffee played a role in the cause of coronary heart problems. In this study coffee was absolved.

But the total picture is by no means clear. In the New England Journal of Medicine, a most prestigious magazine, Dr. Hershel Jick and a large group of co-workers demonstrated "a positive association between coffee consumption and acute myocardial infarction in an analysis of 12,759 hospitalized patients.

"As compared with those who drink no coffee, the risks of infarction (heart attack) among those drinking one to six or more cups of coffee a day are estimated to be increased by 60 per cent or more."

An incidental finding showed there was "no evidence of a positive association between tea drinking and acute myocardial infarction."

Dr. Jick's study was a highly comprehensive one, done at the Boston University Medical Center, and probably is the most elaborate effort of its kind.

Despite the confusion that these two points of view present, it is apparent that caffeine used in excess must be considered detrimental to health.

Caffeine is recognized as a chemical stimulant. Large amounts can produce restlessness, insomnia, palpitations of the heart, anxiety, and can increase the hydrochloric acid secretions in the stomach.

Moderation is therefore advisable intil there is complete and unequivocal knowledge about the exact relationship between coffee and heart attacks.

The chief concerns over caffeine have been those attributed to other drugs and foodstuffs: the possible cardiovascular actions; the presumptive mutagenic and teratogenic effects; and a relationship to bladder or lower urinary tract cancer. Gastric ulcer has also been attributed to caffeine. In the bladder carcinogenic instance, an excerpt from Newsweek, 12 July (3612) is repeated:

What—Coffee, Too?

With the link between cigarettes and lung cancer already firmly established, it seemed only a matter of time before the epidemiologists would get around to showing that another breakfast tradition, the morning cup of coffee, may pose some dire hazards of its own. Coffee, in fact, has for some time been suspected as a promoter of heart disease; and now in the British journal Lancet, a Harvard researcher reports that it may also be linked to cancer of the bladder—particularly in women.

Dr. Philip Cole of the Harvard School of Public Health based his opinion on interviews with 445 patients with bladder cancer and a like number of healthy individuals in the Boston-Brockton area of Massachusetts. Cole's intent was to examine the relationship between bladder cancer, smoking and "occupational" hazards, but he also asked his subjects whether or not they drank coffee. The results showed that for women who drank one or more cups of coffee a day, the risk of developing bladder cancer was two and a half times greater than for those who drank less than this or none at all.

Suspect: Among men, Cole found the bladder-cancer risk was about 25 per cent higher in coffee drinkers, a figure that was not, in his words, "statistically significant." Yet, should a cause-and-effect relationship between coffee and bladder cancer be proved, the effect of coffee drinking on men would be just as great as it is on women, in terms of the total cancer problem. The reason: bladder cancer is four times more common in men than in women.

Cole doesn't know just what it is about coffee that could lead to bladder cancer. Caffeine is a likely suspect, he notes, because it has been shown to cause mutations in cells in tissue cultures. But he adds that the problem may not be related directly to coffee at all. It could be artificial sweeteners such as cyclamates which have, in fact, now been taken off the market because of evidence that they caused bladder cancer in animals. In view of this, Cole points out that no one should become alarmed because of his study until the association between coffee and cancer has been confirmed by other studies.

Durham et al. (825) in a 1968 report on cancer of the urinary bladder found a significant correlation between coffee consumption and bladder cancer among Negro females only, in a study of four race-sex groups in New Orleans, Louisiana.

A recent review of the cardiovascular actions of caffeine and coffee in animals and man by Riker and Kensler (2656) in 1967, includes 283 references, and the authors conclude: "There is no a priori reason to assume that chronic effects of coffee-drinking, if such exist, are attributable to caffeine. Therefore it seems highly desirable to establish both the acute and chronic effects of coffee components other than caffeine."

An earlier paper (1963), however, by Paul et al. (2469) in a "Longitudinal Study of Coronary Heart Disease" involved statistical data from medical case histories of heart disease, family histories, diet, physical activity, psychological factors, etc., and stated that a "positive relation was encountered, however, between coffee intake and coronary disease."

Jick et al. (1563) in a report from the Boston Collaborative Drug Surveillance Program in 1973 have added fuel to the controversial aspects of coffee as related to coronary heart disease, with an analysis of data from a multipurpose survey of 12,759 hospital patients among whom 440 had diagnoses of acute myocardial infarction. The report abstract states "As compared with those who drink no coffee, the risks of infarction among those drinking one to five and six or more cups of coffee per day are estimated to be increased by 60 and 120 percent, respectively." All other factors, including hypertension, smoking or sugar, etc., which have been purported to be etiologic to coronary heart disease were found to have negative association.

A few months later, "Letters to the Editor" (1564) in the same journal in which Jick's report appeared show mixed reactions; the letters are included at this point:

COFFEE AND MYOCARDIAL INFARCTION

To the Editor: We read with much interest the studies on coffee and myocardial infarction reported by Jick and his colleagues (N Engl J Med 289:63-67, 1973) with an attempt at more extensive statistical confirmation of an earlier publication (Lancet 2:1278-1281, 1972) from the Boston Collaborative Drug Surveillance Program. If the comparative studies on the effects of coffee and tea consumption are free from error, it appears outwardly that the pharmacologic effects of the caffeine ingredient are not contributory.

There is compelling evidence, however, that like other methyl xanthine compounds, caffeine has several pharmacologic actions, some of which directly and indirectly involve the heart.[1] Therefore, in a consideration of explanations for an association between coffee consumption and myocardial infarction, other pharmacologic actions of caffeine cannot be avoided.

In experiments carried out in our laboratory administering methyl xanthine drugs (theophylline, theophylline ethylenediamine and caffeine) intravenously and by mouth in man, we found definite increases in the urinary excretion of catecholamines (epinephrine excretion rate being greater than norepinephrine).[2,3] Thus, a catecholamine-releasing action from the adrenal glands by methyl xanthines is a noteworthy effect.[4] Subsequent observations in our laboratory in heart perfusions using methyl xanthines (in repeated doses) indicated that these drugs can also release norepinephrine from the heart (unpublished observations). This response was confirmed by labeling the cardiac norepinephrine stores with ^{3}H-norepinephrine and following their rate of decline after repeated doses of theophylline.[5] Similarly, effects of caffeine on mammalian atrial muscle and interaction with adenosine and calcium have also been shown.[6] Subsequently, the effects of methyl xanthines on the chronotropic action in the dog heart-lung preparation,[7] on the rat heart,[8] on blood sugar[9] and on cardiac phosphorylase[10] confirm evidence for the consideration of an adrenergic component in the pharmacologic action of caffeine and theophylline. Furthermore, the inhibition of chronotropic effects of theophylline ethylenediamine by beta-adrenergic blocking agents and the reduction of response to theophylline ethylenediamine by pre-treatment with reserpine both suggest that cardiac stimulation is due, at least in part, to release of endogenous catecholamines. However, the relative importance of these effects as compared to the action of methyl xanthines independent of adrenergic mechanisms is not known.

In view of these observations studies involving caffeine and its effects on the heart must take into consideration all the known pharmacologic actions of caffeine.

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To the Editor: The article and editorial on coffee and coronary disease in the edition of July 12 remind me of the scientist and his flea circus. He had trained them to jump when he played his phonograph record of John Phillip Sousa's "Stars and Stripes Forever." He cut off the legs on one side, and lo and behold they jumped sideways. He cut off the other legs and lo and behold they did not jump at all. He concluded from this observation that cutting off both legs made them deaf.

It should be obvious that the persons who drink much coffee are the same persons with the type of personality that has been shown to be associated with a high incidence of myocardial infarction. Something so obvious should be investigated before one delves into the labyrinth of pharmacologic mechanisms.

The additional finding that tea drinkers are not similarly affected seems to corroborate the postulate that it is the personality and not the coffee that is responsible since the personality type is usually not associated with tea drinking. Perhaps those in a tea-drinking country such as England might dispute this fact.

Corona, Cal. JOHN H. KONING, M.D.

To the Editor: Although the study, "Coffee and Myocardial Infarction" (N Engl J Med 289:63, 1973), has shown controls that eliminate multiple confounding factors, the authors make only the briefest note that "data on factors such as personality, diet, and exercise were not available for analysis." Not even mentioned in their article is the relevance of the family history. That strong family history of heart disease suggests future heart trouble for the unfortunate offspring is well accepted teaching in medical schools and leading textbooks.[1] That diet, particularly cholesterol and saturated fatty acids, predisposes to coronary heart disease was shown in 1956[2] and many times since. Morris and Gardner, in 1969, identified personality structure as contributing to atherosclerosis,[3] and Dawber et al. found that fatal ischemic disease was encountered less often in physically fit persons than in the sedentary.[4]

Before we all stop drinking coffee and declare it yet another forbidden food, along with eggs and saturated fats, the volumes of earlier research demand that we examine the importance of the above data omission. In their study Jick and his co-workers do not consider the possibility that those who chose to drink no coffee at all very probably have other dietary preferences as well. It is our impression that the members of this coffee-rich society who prefer to have not even one cup per day are often characterized by a personality different from their peers. It is not unlikely, either, that noncoffee drinkers choose to do so on premises that lead them into more healthful exercise patterns.

Jick et al. gloss over serious confounding factors in their study. The strength with which the authors suggest a role for coffee in myocardial infarction may prevent thousands of medical students from enjoying their sometimes elixir of life, may raise the demand and price of tea but, most seriously, may shift the focus of American eating and life habits away from the most solidly proved accelerators of coronary disease – such as diet – and toward this recent observation of considerably lesser importance.

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To the Editor: As Jick et al. point out in their recent article (N Engl J Med 289:63, 1973), the majority of persons suffering acute myocardial infarction die either before or during hospitalization. Thus, contrary to the authors' conclusions, it is possible that coffee drinking is positively correlated with survival rather than incidence rate of myocardial infarction. Data on coffee intake of persons not surviving myocardial infarctions gathered from family and friends would have been useful in the interpretation of this study.

Moreover, patients were classified as zero, intermediate or heavy coffee drinkers on the basis of consumption during the three-month period before hospitalization, although exposure to coffee temptation ranged from approximately 20 to 50 years. Since no data were demonstrated for the underlying assumption that recent coffee intake accurately reflects long years of past possible use, the conclusions do not necessarily apply to chronic coffee drinking (or abstinence) in the general population.

JUDITH GREEN FRIEDMAN, PH.D.
Addiction Research and Treatment Corporation
New York, N.Y.

To the Editor: I agree with the statement of Drs. Kannel and Dawber, in their editorial, that the methodology of the Jick study allows one to say people with myocardial infarctions are more apt to have been coffee drinkers than people without, but not that coffee drinkers are more apt to get myocardial infarctions. I also agree with Dr. Jick in that it is important to publish this type of study, which yields a lead for other prospective studies to confirm.

There are many other medical problems for which solutions are based solely on the same type of retrospective, case-control studies as reported here. These include oral contraceptives and thromboembolism, cancer of the cervix and lack of circumcision, etc. If we really believe Kannel and Dawber we should believe there might be nothing to these other relations based on studies designed in the same way. On the other hand, if we believe the results from the Jick type of study we will all soon be reduced to drinking only water (distilled), eating only ice made from distilled water, and procreating by artificial insemination.

STANLEY SCHOR
Philadelphia, Pa. Temple University School of Medicine

To the Editor: Risk of certain cardiovascular diseases is positively associated with use of coffee, tobacco, oral antidiabetic drugs, with elevated blood glucose level, and exposure to certain air pollutants.[1,2] Also, coffee drinkers tend to be cigarette smokers.[3] Although caffeine is the principal methylxanthine of both coffee and tea, the risk is not evident for tea usage.[1,3]

Since statistics can reject but cannot validate hypotheses,[2,4,5] physiologic explanations for the associations are required. Moreover, a presumed cause may in reality be an effect – alternatives that are not resolvable by subjective judgment.[2,4]

At least two hypotheses can explain the association between coffee use and risk of acute myocardial infarction: coffee causes infarction; and coffee use and infarction risk are both "influenced by a common cause – the individual constitution or genotype."[4] Degree of use of coffee, tea and tobacco is largely self-selected, not randomly selected, resulting in biased usage subgroups that present special problems in hypothesis testing.[2,4,5]

Caffeine, theophylline and nicotine affect biogenic amine physiology, glucose metabolism, bioenergetics and behavior,[2,5] thus providing a prospective physiologic explanation for the associations. Self-selected use patterns can be influenced by ethologic homeostatic processes.[2] Use may thus be an effect or symptom of constitutional deficiency that influences disease risk, in accord with the second hypothesis advanced above, to the extent that the products do not alle-

viate the deficiencies.[2] Inferences from statistics that coffee is harmful to the heart, and tea beneficial, and that caffeine is not involved[1,3] are invalid.[2,4,5] Studies that do not consider physiologic homeostasis[1,5,6] (W. B. Cannon), ethologic homeostasis or genetic heterogeneity of populations can be misleading. Individual human responses to coffee vary from increased euphoria among users to dysphoria among nonusers and among deprived users.[7]

Adenine, present in tea to a greater extent than in coffee, was reported to depress biologic effects of caffeine,[8] a finding needing confirmation. Since adenine and methylxanthines are all purines, molecular competition in neurophysiology might be involved.

A self-selected, coffee-drinking subgroup of people may exist that is constitutionally more likely to accumulate mutations, incur angina and acute myocardial infarction and smoke cigarettes than noncoffee drinkers.[4]

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To the Editor: With the recent accumulation of data relating coffee consumption to myocardial infarctions, I thought it might be of interest to bring forth yet another statistically significant relation. During my sophomore year (1971) at the Medical College of Wisconsin, I did a study (as part of the preventive-medicine course requirements) in which I compared the apparent per capita coffee consumption to the mortality rate due to "arteriosclerotic-degenerative heart disease" between different countries. All data for this study were taken directly from the United Nations Statistical Yearbooks and the United Nations Demographic Yearbooks.

For the total of 16 countries for which sufficient and significant data were available the correlation coefficient between the apparent per capita coffee consumption and deaths per 100,000 from arteriosclerotic and degenerative heart disease was calculated to be $r = 0.763$ ($p<0.01$) for the years 1965-66. When countries whose populations were grossly related with respect to diet and climate (data also available from the United Nations Yearbooks) were compared, the relation became even more significant – for example, for Belgium, Netherlands, Norway, Finland, Denmark and Sweden, $r = 0.990$ ($p<0.005$), and for Japan, Greece, Portugal, Israel and Italy, $r = 0.974$ ($p<0.01$).

Although the indexes used in this study were indeed gross, the results are perhaps significant enough to warrant further investigation along this avenue.

Milwaukee, Wisc. GEZA PALOTAS

A critical comment on Jick et al. appearing concurrently; is a report by Kannel and Dawler (1620) which is presented in its entirety:

COFFEE AND CORONARY DISEASE

CURRENT assessment of the epidemiology of coronary heart disease indicates a major role of environment in the evolution of this disease. Environmental factors that contribute to the incidence of the disease include dietary habits, cigarette smoking and physical activity. The present issue of the *Journal* contains an article incriminating coffee drinking as a factor in the development of coronary heart disease. The report of Jick et al. involves a study of coffee consumption by a large number of hospitalized subjects with a discharge diagnosis of myocardial infarction as compared with subjects hospitalized for other reasons. The findings indicate a higher coffee intake among the patients with myocardial infarction before the episode leading to hospitalization. From these findings the authors estimated that coffee drinkers were at a twofold increased risk of development of infarction.

The report, "Coffee and Myocardial Infarction," confirms a previous one[1] but is in disagreement with data from prospective studies. Curiously enough, coffee is associated with myocardial infarction, but tea is not. As with almost all retrospective studies the subjects investigated constituted only those with myocardial infarction who survived long enough to be hospitalized. This group of patients experienced a mortality rate of only 4 per cent. Such a sample is hardly respresentative of this highly lethal disease.

The Achilles heel of any retrospective study is the control group against which the subjects with disease are to be compared. Jick et al. used discharged hospitalized patients. Such a population may contain an excessive number of subjects with gastrointestinal or other diseases in which coffee drinking has been either voluntarily abandoned or medically proscribed. Thus, the coffee consumption of a hospitalized population cannot be accepted unequivocally as representative of the habits of the general population.

Although retrospective studies are of proved value in the development of hypotheses, for more definitive studies they seldom provide conclusive evidence regarding real differences between those in whom a disease develops and those remaining free of it. To test the hypothesis, it is usually necessary to observe the development of the disease in a general population. Such studies avoid any distortion in selection of either disease or control groups.

The relation of coffee intake to coronary heart disease in general and myocardial infarction in particular has already been investigated in a number of prospective studies such as Framingham, Chicago and elsewhere. The prospective studies of which we are aware either have failed to find any association between coffee intake and myocardial infarction or have observed an associated characteristic that could account for the relation. In these prospective studies no relation of antecedent coffee intake to subsequent myocardial infarction, regardless of outcome, has been observed.

How consistent is the evidence linking coffee to the

occurrence of myocardial infarction in retrospective studies? Some have found no difference,[1] and others have found an excessive intake of tea and less of coffee in subjects with myocardial infarction.[2]

The pharmacologic basis that suggested a possible relation between coffee or tea and the development of coronary heart disease was the xanthine content of these beverages. Both coffee and tea contain caffeine, and tea contains theophylline. The finding of Jick and his associates that tea is innocuous and coffee harmful to the cardiovascular system is paradoxical. This observation led these authors to blame some other unknown ingredient in coffee. Other investigators have suggested the harmful effects of sucrose or cream in the coffee — or associated cigarette smoking.[3]

Even if we accept caffeine intake as a possible mechanism by which coffee exerts an adverse influence on the cardiovascular system we find that studies of the acute effect of caffeine on the cardiovascular system have shown only minor increases in blood pressure and heart rate. Dilatation of the coronary vessels is counterbalanced by the increased demand imposed by slight stimulation of the myocardium. The chronic effects of coffee intake are at present unknown, but tolerance certainly develops. Contradictory effects on atherogenesis have been reported.

It is a common lament that almost everything that one enjoys in life is either illegal, immoral or fattening. To these we must add — and hazardous to the heart. Must we now forgo the traditional coffee break and morning cup of coffee? The retrospective data presented by Jick et al. suggest that we should.

However, careful examination of all the evidence would counsel against drawing premature conclusions. Jick and his associates apparently concur in this, for they show laudable restraint in interpreting their data. Paul, who provided the first prospective data seeming to incriminate coffee, has also advised caution. In fact, in multivariate analysis his data suggest that cigarette smokers who drink coffee are better off.[6] Clearly, more evidence is needed before we can confidently add coffee to the growing list of faulty living habits that must be curtailed in the quest for a lower coronary incidence. We are faced with a formidable enough task in having to engineer physical activity back into daily living, change cigarette-smoking habits and modify the national diet. We should not complicate the problem further by advocating premature restrictions of other pleasurable habits unless there is equally good evidence that such a change is warranted.

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A brief report by Hickey et al. (1402) in 1973 presents an argument in which the various factors which have been associated with cardiovascular disease represent "a self-selected subgroup of people" who are constitutionally more likely to drink coffee, incur certain cardiovascular diseases and accumulate somatic mutations than non-coffee drinkers; the subgroup may also be more likely to be cigarette smokers.

Mulvihill (2266) has reviewed the literature in 1973 on caffeine as a teratogen and mutagen, summarizing in tabular form studies of teratogenicity from 1960 to 1972. Genetic or chromosomal changes following exposure to caffeine have been observed in plants, reported controversially in Drosophila, and associated with spermatozoa in mice. Delayed mitosis in human lymphocytes (cultured) and chromatid breaks have been reported.

An article of general interest, entitled "Do Have Some Coffee Before You Leave" appeared in the Journal of Food and Cosmetics Toxicology (3613) in 1972 (Anonymous), and contains a review of experimental findings relative to absorption and fate of ingested caffeine, mutagenicity, serum lipid levels, metabolic and physiological effects and allergy to tea and coffee.

Heyden and Escher (1397) have reviewed the evidence of the effects of "coffee consumption from a medical viewpoint". They saw no reason for restricting coffee consumption by patients with gout, diabetes or primary and secondary heart infarcts.

Bucko (443) in 1972 also reviewed the evidence of the importance of coffee in man (the "intellectual") and concluded: "It can be affirmed that coffee is a most innocent means of toxicomania, it forms no habit, causes no symptoms of a change in habits and does not at all change the personality and the human character". It was noted in Bucko's paper that coffee is complex, containing besides caffeine many diverse substances; caffeine is not found in coffee in a free form, but fixed with potassium and chlorogenic acid complexes. Caffeic acid, quinic acid, trigonelline, coffee fat and choline are also components of coffee, but it is believed that caffeine is probably the only active principle.

Muller and Jernikos-Danellis (2264) in 1970 determined the influence of the environmental temperature on the LD_{50} of caffeine in mice. The animals were exposed one or three hours to temperatures of 15 degrees, 22 degrees and 30 degrees C before intraperitoneal injection of caffeine: no difference was observed with regard to the length of preinjection exposure (1-3 hrs), but significant differences were observed related to the temperature changes, the toxicity being decreased at both lower (15 degrees C) and higher (30 degrees C) temperatures relative to tha normal 22 degrees C. The variations in the 1 hour preinjection LD_{50}'s ranged from about 180 mg/kg at 30 degrees C to about 274 mg/kg at 22 degrees C and 244 mg/kg at 15 degrees C.

Sensitivity variations in LD_{50} doses of caffeine given to normal and to hereditary-obese mice were studied by Kuftinec and Mayer (1828) in 1964. The LD_{50} for normal lean mice was found to be 400 mg/kg; the LD_{50} for obese hyperglycemic mice was 80 mg/kg.

Comparison of intravenous commercial "natural" caffeine and synthetic caffeine doses for an LD_{50} for mice by Scott et al. (2902) showed no statistically significant difference: the commercial LD_{50} was 79.36 plus or minus 6.94 mg/kg; the synthetic caffeine LD_{50} was 75.51 plus or minus 5.39 mg/kg.

McColl et al. (2116) in 1956 determined the LD_{50} for caffeine in mice given intraperitoneally to be 525 mg/kg: given orally, the LD_{50} was 878 mg/kg.

Beliles (222) in 1972 studied the effects of pregnancy in mice on the LD_{50} of caffeine. The LD_{50} for nonpregnant mice was found to be about 89 mg/kg and for pregnant mice, about 96 mg/kg; the difference was not significant.

The effects of age on caffeine toxicity in rats was reported by Poe and Johnson (2528) in 1953. Young rats, 1.5 months old showed an LD_{50} of 200 mg/kg; rats 2-4 months of age, LD_{50} was 205 mg/kg; old animals, LD_{50} was 167 mg/kg. The toxicity of caffeine appeared slightly greater for older animals.

Boyd (389) in 1959 reported an oral LD_{50} in female albino rats of 192 plus or minus 18 mg/kg. The clinical and pathological signs of caffeine poisoning were detailed. A year later, Boyd (390) reported a similar study on guinea pigs which showed an oral LD_{50} of 230 plus or minus 21 mg/kg. The clinical signs were similar to those observed in the rat. Boyd et al. (394) repeated the earlier experiment with female albino rats, but with emphasis on the chronic oral toxicity of caffeine. As a preliminary to the study, the acute oral LD_{50} was determined to be 264 plus or minus 10 mg/kg, the animals not having been fasted before treatment.

Wigderson (3485) in 1956 described a case of fatal poisoning of a 15 pound, 4 month old dog that ingested about 3.25 g of caffeine and died within several hours.

Jokela and Vartiainen (1571) reported in 1959 a case of accidental death of a female hospital patient who was given several injections intravenously of about 3.2 g caffeine in a solution thought to be glucose. A similar case involving a woman who drank my mistake a solution containing about 19 g caffeine was reported by Khodasevich (1669) in 1957; she died within 30 minutes. A general discussion of caffeine toxicity in humans is included in the report; doses of 1 g or more produce severe symptoms but with usually rapid recovery. A suggested fatal dose for humans was about 10 g caffeine.

Bachmann et al. (141) found no growth retardation in weanling rats of both sexes when fed 40-50 mg/kg/day caffeine for 26 weeks (10 males) or 11 weeks (10 females). The experiment was chiefly designed to demonstrate the influence of prolonged caffeine administration on reproductive functions and is detailed in the Biological Data, Section IV.

The influence of starvation or inanition on the toxicity of caffeine was studied by Peters (2492) in 1966 using female Wistar albino rats. A

variety of treatments from normal diets with and without caffeine (185 mg/kg/day) to reduced diets plus caffeine continued for 14 days. Reducing food intake increased the caffeine toxicity, but in general the effect is not appreciable until the partial diet approaches zero intake.

Peters and Boyd (2496) in 1967 performed a similar experiment with cachexigenic diets given rats, anticipating similar results in the toxicity of caffeine. The diet consisted of a rancid, biotin-deficient raw egg-white; the caffeine dose was again 185 mg/kg/day. After two months, the results were "paradoxical", in that the cachexigenic diet increased the sensitivity of rats to caffeine toxicity, but those animals receiving normal diets plus caffeine died earlier.

The chronic oral toxicity of caffeine in Wistar rats was studied by Boyd et al. (394) in 1965 (see also same reference, Biological Data, Section I). Decreasing fractions of the previously determined LD_{50} dose were given intragastrically 5 days a week for 100 days, or until death, which ever occurred first. Three LD's were determined (each based on 0.1 the normal life span, or 100/1000 days): an LD_{100} (0.1L); an LD_{50} (0.1L); and LD_0 (0.1L). In that order, the doses of caffeine for the rat were found to be: 191 plus or minus 5.7 mg/kg; 150 plus or minus 3.1 mg/kg; and 110 plus or minus 2.5 mg/kg. Symptoms preceding death, and histopathologies are detailed.

Scott and Chen (2900) in 1944 made comparative studies on the effects of caffeine and theobromine in rat and man (see also Biological Data, Section IV). Rats received varying percentages of the caffeine in the food, varying from 0.02 to 0.5%; of the 5 animals tested on 0.5% caffeine, autopsy (after 28 days) showed 3 normal, 1 showed some pulmonary edema and congestion, and 1 case of hydronephrosis but with no stones.

Peters and Boyd (2495) in 1967 reported that studies with rats in experiments to determine the effects of age and sex on caffeine toxicity indicated slight influence of sex and slight influence of age (older males were more sensitive to caffeine toxicity than younger females).

In a study investigating a possible relationship between caffeine ingestion and the pathogenesis of peptic ulcers, Roth and Ivy (2716) in 1944 employed a mixture of caffeine, beeswax and mineral oil injected intramuscularly in cats. Daily injections containing 300 mg caffeine for about 10 days resulted in total doses to each of 22 experimental animals of about 1 g/kg body weight. Half the animals developed bleeding erosions or ulcers in the stomach mucosae of antrum and prepylorus; multiple lesions were seen in 5 of the cats. It was suggested that caffeine-type beverages be restricted in the management of peptic ulcer patients.

Few instances of severe caffeine poisoning in humans have been reported. Reimann (2623) reported in 1967 a case involving a woman who had chronic symptoms of caffeine poisoning, - low grade fever, anorexia and irritability, presumably due to a daily consumption of 15-18 cups of coffee. The symptoms disappeared upon reduction of coffee-intake to a cup a day.

Goodman and Gilman (1155) in 1970 reviewed the pharmacology of the xanthines in a text devoted to the pharmacological basis of therapeutics.

The treatment of caffeine has been included in Biological Data, Section IV.

Coffee drinking has been suspected, along with other factors such as smoking, high cholesterol diets and sugar, etc. as etiologically associated with myocardial infarction and other cardiovascular diseases. Klatsky et al. (1700) in 1973 surveyed 464 case histories involving myocardial infarction in considerable detail, carefully eliminating factors other than coffee in the case etiologies. The results of the study, however, while indicating a possible relationship between coffee consumption and myocardial infarction, was confused by a strong correlation between smoking and coffee consumption.

Little et al. (1964) in 1966 reported that a positive correlation was demonstrated to exist between elevated serum lipids in coffee drinking patients with coronary heart disease that could not be demonstrated in healthy controls. Tea did not produce the same results in heart disease patients as did coffee; since tea also contains caffeine, the authors suggested that caffeine was not responsible for the elevated serum lipid levels in coronary heart disease patients.

Walker and Gregoratos (3430) in 1967 found no significant correlation between coffee consumption and myocardial infarction in a study of 100 men who had survived myocardial infarctions.

Paul (2468) in 1968 noted the conflict in experimental data regarding the role of caffeine in heart disease. He did demonstrate a relationship between angina pectoris (and myocardial infarction) to a consumption of 5 or more cups of coffee daily, but the death rate among 1700 men studied was higher among those who did not drink coffee or who drank moderately, fewer than 5 cups daily.

Saytanov (2827) reported in 1971 a case in which a worker was exposed to a large quantity of powdered caffeine sodium benzoate. Inhalation exposure produced symptoms of chest pains, heart palpitations, chills, cramps, etc.; the myocardial disturbances were thought to be due to release of catecholamines which in excess in heart muscle would result in necrosis and hypoxia. The poisoning was not fatal and recovery was complete in several weeks.

Jick et al. (1562) in 1972 reported the results of studies by the Boston Collaborative Drug Surveillance Program on the relationship of myocardial infarction and coffee intake. The studies showed that a coffee intake exceeding 5 cups daily resulted in a risk of myocardial infarction twice that of non-coffee drinkers. Tea, which also contains caffeine could not be similarly correlated to myocardial infarction. This made a positive correlation between coffee and infarction difficult. The study presumably ruled out an influence of cigarette smoking in myocardial infarction.

Numerous studies of the possible mutagenicity of caffeine in mice have been reported. Thayer and Kensler (3220) in 1973 fed male mice caffeine in the drinking water for 8 weeks at levels of from 3.6 to

to 122 mg/kg daily, after which the males were mated to untreated females; the only notable effect was a reduced fertility among the males. The mutation index data from females and offspring were not significant. The enhancement of radiation-induced dominant lethal mutations by caffeine in gamma ray-irradiated male mice, or in mice given triethylene melamine (TEM) was not demonstrated.

Cattanach (517) in 1962 found negative results in efforts to induce translocations in mouse chromosomes of the type reducing male fertility. Male mice given 0.3% caffeine in the drinking water for several months were bred to virgin females and several subsequent generations of male offspring were tested for fertility. Only in the original caffeine-treated parents was there some reduction in fertility, but this effect diminished upon cessation of the caffeine treatment.

Mouse testes cultured in vitro in a saturated caffeine solution showed chromosomal aberrations (stickiness, clumping, fragmentation, etc.) in spermatagonial cells and also abnormalities in mature sperm in a study by Slizynski (3007) in 1971.

A description of the dominant-lethal assay technique in mammalian studies, in measurement of the effects of chemical mutagens was presented by Epstein et al. (884) in 1970. As consequences of chromosomal damage in the male treated with a mutagen, subsequent matings produce effects that serve as indicators of the damage: numbers of fetal implants, pre-implantation losses, sterility or partial sterility, early and late fetal deaths; the latter is the truest indication of mutagenicity, according to Epstein. The author, together with Shafner (Epstein and Shafner, (883)) had described the use of the dominant lethal test using mice. A mutagenic index, based on the number of fetal deaths due to the male sperm mutations is calculated by a formula; in an experiment with caffeine, the mutagenic index was zero, or no significant mutagenicity of caffeine was found. Epstein et al. (884) in 1970 used the dominant lethal test for mutagenicity in Swiss male mice of caffeine given both orally in the drinking water and by intraperitoneal injection. The oral dose was 6.4 mg/mouse/day; the injections ranged from 168 to 240 mg/kg. In each instance, the males were bred to virgin females; after 13 days, the females were autopsied and early and late fetal deaths determined. The results were negative with respect to fetal deaths, but the fertility of the treated males was significantly reduced.

Kuhlman et al. (1829) in 1968 suggested that the experimental evidence indicating that caffeine increased dominant lethal mutations in male mice, and not in females, was due to the fact that caffeine affects cells during DNA replication, which is a continuous process only in male spermatogenesis and ceases in the female ovary at the time of birth. The report also reviews other findings in the field of human and mouse mutagenicity of caffeine.

Adler (21, 22) has reported in 1969-1970 reviews of several author's studies of the problem of caffeine mutagenicity: Stieve's research with Russian rabbits, in which males were treated with doses, subcutaneously, of caffeine ranging from 50 to 200 mg/kg, and were mated with untreated females; up to 70% of the litters failed to survive for a week after birth.

(Adler felt that the experiment was inadequately controlled); Cattanach's experiment, which has already been noted, was also included; Lyon, et al. gave both male and female mice 0.1% caffeine in the drinking water for 7 weeks; offspring (F1) were similarly treated with caffeine for 10 weeks and then mated with mice bearing homozygous recessive genes at 7 loci. No evidence of either dominant or recessive mutations was obtained; other experiments also failed to produce evidence of lethal mutations.

Adler (21) had studied in 1969 the mutagenic effects of caffeine on spermatogenesis in male mice given a single dose of 250 mg/kg intraperitoneally, after which the males were mated to virgin females. No significant differences in implantational egg losses were observed, but the males copulated less frequently. Adler and Rohrborn (23) reported in 1969 that caffeine given orally to male mice in concentrations of from 0.0023% to 0.5% produced univalent chromosomes more frequently in the meiotic spermatagonial chromosomes of the treated males than in the controls; the authors regarded this as a fortuitous or chance occurrence rather than an effect of the caffeine.

Roehrborn (2677) in 1972 exposed male mice to chronic, low doses of caffeine for periods of from 245 to 351 days. Three concentrations of caffeine were given in the drinking water: 3.4-3.6, 14.9 and 17.3 mg/kg/day. Virgin females were mated with treated males, and on the 15th day of pregnancy were sacrificed. Using an increased number of dead, uterine implants as the criterion for induced dominant lethal mutations, all efforts to demonstrate a significant effect of caffeine were unsuccessful.

Cytostatic (mitotic inhibiting) properties of caffeine were observed in human lymphocyte cultures by Timson (3237) in 1972. The degree of mitotic inhibition was related to the concentration of the caffeine: 10^{-4} M solutions were ineffective; 10^{-3} M partly inhibiting; and 10^{-2} M solutions completely inhibited mitosis. The author suggested that the mutagenic and cytostatic thresholds are about equal, thus explaining the failure of caffeine to show mutagenic activity; affected germ cells do not divide.

Ostertag et al. (2437) found that caffeine caused chromosome breakage in HeLa cells in culture, proportional to the caffeine concentration up to 10 mg/ml; above this concentration, breakage was increased at a rate greater than linear. Few translocations were observed.

Doses of caffeine varying from 250 to 800 mg/kg were injected subcutaneously into pregnant white mice between the 7th and 14th day of gestation, by Snigorska and Bartel (3024) in 1970. The fetuses from the pregnant mice that survived full term (20 days) showed various developmental abnormalities, particularly in the skeleton. Other disorders seen included subcutaneous hematomas, harelip and fetal resorption. Similar studies by Nishimura and Nakai (2360) in 1960 had produced the same results. Fujii et al. (1044) in 1969 reported the results of a series of experiments in which a 200 mg/kg dose of caffeine was given subcutaneously or intraperitoneally, in a single dose, or in divided doses of 100 mg/kg each separated by 2 or by 4 hours. The female, pregnant mice, were treated on the 12th day of pregnancy and were autopsied 6 days later. The numbers of live fetuses, numbers of fetuses with abnormalities, and the percent abnormalities (cleft palate, micrognatha, digit defects, hematoma and

clubfoot) were tabulated. The teratogenic effects of caffeine were marked. Fujii and Nishmura (1046) in 1972 performed similar experiments on Sprague-Dawley rats. Pregnant females were given various diets containing 0.25 or 0.50% caffeine during early, late or throughout gestation. A considerable number of abnormalities were found; the most severe teratogenic effects resulted from caffeine given during day 8 to 14 of gestation. Severe edema occurred during the 15th to 21st days of gestation. Studies by Bertrand et al. (269) using mice and rats, given oral doses of caffeine of 50 mg/kg during the 6th to 18th day of gestation in the mouse studies, and 75 to 150 mg/kg caffeine during gestation in the rat, produced inconclusive results in the mouse studies, but specific malformations, ectrodactylys, in the rats. The rat anomalies peaked at the caffeine doses of 125-150 mg/kg. Bertrand et al. (268) in 1970 tested various strains of rats, mice and rabbits, producing ectrodactylys in rats, not in mice, but some in rabbits. The studies suggested that the female rat is sensitive to the teratogenous effects of caffeine by virtue of genotype; the anomalies probably being somations rather than mutations.

Teratologic evaluations of caffeine on mice, rats, hamsters and rabbits by Food and Drug Research Laboratories, Inc. (983) in 1973, produced generally negative findings at the following dosages: mice, 36 mg/kg/day for 10 days; rats, 22.5 mg/kg/day for 10 days; hamsters, 30 mg/kg/day for 5 days; and rabbits 7 mg/kg/day for 13 days. In rabbits, at doses of 32.5 mg/kg, maternal mortality increased and fertility decreased, but no teratogenicity was observed.

Goldstein and Warren (1142) in 1962 made a study of more than 200 hospital records of male patients with diagnoses of gastric carcinoma and carcinoma of the colon. Efforts to correlate the cancer incidence with beverages containing caffeine were negative; the author concluded that caffeine probably does not play a significant role in the etiology of gastric carcinomas.

Cole (617) in 1971 reported a positive correlation between bladder cancer and coffee drinking in a study of nearly 500 bladder cancer cases. Information concerning coffee consumption and smoking habits of the patients studied led the author to the belief that about one-third of such cases in the United States could be attributed to coffee drinking; caffeine was not specifically identified as the contributing factor in the correlation to bladder cancer. Timson (3236) in 1971 confirmed Cole's findings, noting also that the coffee-bladder cancer correlation was higher in women than in men, possible due to stimulation of mitosis in cancer cells; Timson had observed that caffeine (coffee) stimulated lymphocyte mitosis to a greater degree in women than in men. Zeitlin (3567) in 1972 stated that Cole's findings in coffee-drinking bladder cancer patients were not supported by laboratory studies. Zeitlin fed coffee to rats for two years without bladder cancers, or other anomalies related to coffee, appearing.

A study of "the alleged role of caffeine in pathogenesis of gastric ulcer" by Gidding's et al. (1109) appeared in 1945. One study used albino rats, given 75 mg/kg caffeine daily orally for from 8 to 20 weeks; microscopic gastric erosions and a single small ulcer were seen, but the effects of caffeine were not significantly different from the control animals. In a second study, 30 cats were intubated with 75 mg/kg caffeine

daily for three weeks without inducing gastric ulcers. Ulcers could only be produced by fatal doses of caffeine - up to 150 mg/kg. The non-ulcer doses of 75 mg/kg were equivalent to a human consumption of about 50 cups of coffee per day. This group of investigators concluded that caffeine-containing beverages do not contribute to gastric ulcers in the human. Pfeiffer and Gass (2506), however, in 1965, produced gastric secretion in rats by intramural injection of caffeine solutions into the submucosa of the everted rat stomach; from this finding, the authors fasted rats, vagotomized one group (vagotomy prevents normal gastric secretion) and injected caffeine intramurally. Gastric secretion occurred in the vagotomized group, and the authors suggested that the role of caffeine in ulcerogenesis is by hyperstimulation of gastric acid secretion.

Thayer and Kensler (3220) in 1973 exposed four generations of mice continuously to caffeine in the drinking water at three dose-levels of 4-5, 12-18 and 25-39 mg/kg/day. Both sexes received the treatment. No consistent, dose-related effects of caffeine on fertility, age at sexual maturity, mean litter size, weight of offspring at weaning, sex ratio or fetal abnormalities were observed.

Bachmann et al. (141) in 1946 tested the influence of a chronic exposure to caffeine on the reproductivity of albino rats, given a sweetened caffeine-containing beverage as the only liquid in the diet over a period of up to 3.5 years. The average dose was about 40-50 mg/kg/day. Mated at 100 days of age, the pairs were kept until the female produced no offspring for a period of 3 months after the last litter. No evidence of sterility, or unusual histological changes in the male testes, were observed.

Gilbert and Pistey (1112) in 1973 studied the effects of intraperitoneally injected caffeine at various dose levels in female rats recently impregnated. Reproductive parameters were determined as a measure of caffeine effect: average litter size, number of resorptions, fetal weight and placental weight. Litter sizes were reduced by increasing doses of caffeine (from 4 to 16 mg daily) as were average fetal weights; the effects were significantly dose-related. No teratologic or abnormal placental changes were observed.

Haldi et al. (1287) in 1947 treated rats with 75 mg/kg caffeine in water by gastric intubation over a 100-day period; after a one-day withdrawal of the caffeine, renewed administration of the caffeine stimulated a spontaneous, marked activity during the half hour following the dosage. Simular results were found when caffeine was given intraperitoneally.

Wistar rats, intoxicated with caffeine given orally in doses of 185 mg/kg daily for 14 days by Peters (2493) in 1967 engaged in hemorrhagic automutilation when isolated. Synthetic diets and starvation increased the automutilation induced by caffeine; the presence of other rats directed the agression away from self to others.

A series of psychological tests evaluating the performance of physical and intellectual tasks by humans, influenced by caffeine, were reviewed by Weiss and Laties (3462) in 1962. Typical findings include: oral or intravenous 500 mg caffeine significantly enhanced performance of physically

exhausting work; reaction time is little or not affected by caffeine; intellectual performance is not improved, but caffeine relieves fatigue and boredom; typing speed increases, errors decrease with caffeine; etc. Lienert and Huber (1952) tested college students in speed and cognitive performance; 300 mg caffeine (1 cup strong coffee) improved speed performance; tests not requiring speed were not, or negatively affected.

Marek (2065) in 1967 found that a single dose of 100 mg/kg caffeine, given either orally or subcutaneously, suppressed experimentally-induced edemas in white rats. The author explained the effect of caffeine on edemas as due to catecholamines released from the adrenal medulla.

Caffeine was found to be goitrogenic in rats by Wolff and Varrone (3511) in 1969. Rats were given a low iodine diet and 10 micromoles (.194 mg) caffeine/g of diet, for 24 days; the thyroid weights increased without a significant decrease in serum protein-bound iodine. The authors suggested that caffeine increases the efficiency of the thyroidal response to the thyroid-stimulating hormone.

Goldstein (1138) in 1964, using a double-blind design in a study of several hundred medical students, found evidence that caffeine does prolong the time required to fall asleep. Regular coffee drinkers were less affected, and some experienced headache in the morning after abstaining from coffee for 18 hours. The author reported in 1969 (Goldstein et al. (1144)) similar but more detailed studies of the psychotropic effects of caffeine in man. It was found that the physiological and psychological effects of caffeine in humans were different in those who are habituated and those who are abstainers.

Schulte (2882) related a personal reaction to excessive coffee and tea consumption (dozen or more cups of strong coffee or tea in a 3-day period). He suffered entoptic scotomas and hemianopsia, and severe headaches. A fellow physician suffered similar symptoms after several cups of strong coffee. The explanation given was a probable spasm of the blood vessels in the brain, alternately dilating and constricting the vessels, producing the visual phenomena. Diamond and Cole (761) in 1970 found that about 100-200 mg caffeine given orally to several human subjects caused a dose-related decrease in the visual threshold; caffeine enhanced the absolute visual sensitivity.

Dreisbach et al. (807) in a study of caffeine habituation in 1943, gave human subjects increasing doses of from 120 to 780 mg per day for 6 or 7 days and then substituted placebos without the subject's knowledge. Withdrawal symptoms, consisting of severe headaches, characterized more than half the trials. Blood samples showed a decrease in serum calcium and an increase in serum phosphorus accompanying the withdrawal headaches.

Fujii et al. (1047) in 1972 tested the effects of caffeine on the running performance of race horses. Injected doses of between 2.5 g and 5.0 g were effective in reducing drowsiness in the animals; heart beat was increased with arrhythmic signs, and the impulse to run was enhanced.

Burg and Werner (468) reported in 1972 on the distribution of caffeine and its metabolites. Mice were used in the study, and doubly-labeled

caffeine with radioactive C^{14} and H^{3} isotopes, orally intubated, permitted tracing the subsequent metabolic events. The caffeine was given in doses of either 5 or 24 mg/kg and the animals were sacrificed at various times of up to 24 hours after dosing. Other mice received caffeine for 8 months in drinking water before dosing with the radioactive caffeine. Various organs were treated for counting radioactivity in a scintillation spectrometer; other tissue homogenates were studied by paper chromatography and radiochromatogram scanner. Within 5 minutes of dosing, caffeine rapidly entered organs and tissues; at 30 minutes the major metabolite was 1,7-dimethylxanthine. At later times (greater than one hour), caffeine, 1,7-dimethylxanthine and 1-methyluric acid were present in liver, lungs, kidneys, testes and plasma. By 8 hours and at 24 hours, the levels of radioactivity had fallen so low that identification of metabolites was difficult. There were indications that a barrier in brain and testes prevented accumulation of caffeine in those organs. The half-life of caffeine in all organs was less than 3 hours.

The plasma level time-courses of caffeine in male human subjects, given caffeine orally, intramuscularly, or intravenously was studied by Sant'Ambrogio et al. (2795) in 1964. Doses varied from 6 to 9 mg/kg. Blood samples were taken at various intervals and the plasma levels of caffeine were determined. After oral administration, the plasma levels of caffeine peaked at 30 minutes; intramuscular injection produced peaks at 60 minutes. Intravenous injections of caffeine diffused through the vascular walls very rapidly; the half-time was about 1.5 minutes. The overall biotransformation or metabolism rate was determined to have an average half-reaction time of about 3 hours.

Axelrod and Reichenthal (134) in 1953 performed similar studies of the fate of caffeine in man. Oral doses of 7 mg/kg caffeine in 3 men showed a peak plasma level at about an hour after dosing. A dose of 500 mg caffeine given intravenously resulted in urine analyses indicating only about 0.5 to 1.5% excreted unchanged. A 7 mg/kg intravenous dose of caffeine showed a half-value time of about 3.5 hours in the plasma levels (range from 2.5 to 4.5 hours from subject to subject). A similar finding in dogs given 4 mg/kg intravenously was observed, the half-value time averaging about 5 hours. Other studies with dogs showed a distribution of caffeine given intravenously to be distributed in approximate proportion to the water content of the tissues.

For the mutagenic aspects of caffeine demonstrated in lower organisms to be of concern to man, it must be shown that caffeine has ready access to the germinal tissue. Goldstein and Warren (1141) in 1962 using testes and ovaries obtained as surgical specimens from patients undergoing orchidectomy or oophorectomy, and aborted fetuses, determined that the germ cells of regular coffee or tea drinkers are bathed in caffeine solutions equivalent to a continuous exposure to about one microgram per milliliter. Fetal gonad cells in the pregnant woman would be similarly exposed.

The disposition of caffeine in the body tissues of a presumed suicide was determined by Parish et al. (2461) in 1965 to be distributed in the tissues in the following sequence, from greatest concentration to least: stomach, liver, kidney and brain. Comparative studies of rats given 1 g/kg caffeine orally showed a distribution of caffeine in the rat tissues similar to that in man.

Burg and Stein (467) in 1972 selected the mouse and radioactively labelled caffeine for studies of the urinary excretion of caffeine and its metabolites. Carbon-14 and tritium in the ratio of 1 microcurie of C^{14} to 50 microcuries of H^3, in C^{14}-caffeine-1-methyl and generally labeled tritium caffeine, provided a tracer technique for the metabolic studies. The procedure was similar to that described in the same paper under section II, Absorption-Distribution. The caffeine was given orally and air samples, urine and feces were periodically collected for assay of radioactivity in the scintillation spectrometer. The main excretory route was the urinary; some C^{14} and less H^3 was recovered from the expired air of the animals, and caffeine itself was almost entirely absorbed in the gastrointestinal tract with little appearing in the feces. Of the total radioactivity of the caffeine given to mice, 64-90% was recovered in the urine, chiefly as metabolites: 1,7-dimethylxanthine; 3-methylxanthine; 7-methylxanthine; 1-3-dimethyluric acid and 1-methyluric acid. Only 3-6% of the total administered caffeine appeared in the urine as caffeine. Within 8 hours of dosing with 25 mg/kg of radio-labelled caffeine, 80% of the metabolites had been excreted in the urine.

Buchanan et al. (437) in 1945 investigated the possibility that some caffeine metabolites are further converted to uric acid; some investigators had reported an increased uric acid excretion following caffeine and theophylline ingestion (coffee and tea) but not from theobromine (cocoa). Using a uricase enzymatic procedure, the authors demonstrated that the xanthines have little effect on the excretion of true uric acid over 24-hour periods. Weinfeld and Christman (3460) studied the urinary metabolites of human subjects given 1 gram doses of caffeine and found no appreciable uric acid excretion. The metabolite, 1,7-dimethylxanthine of caffeine yields the 1-methylxanthine and 7-methylxanthine; the 1-methylxanthine is further metabolized to 1-methyluric acid according to a scheme postulated by the authors.

A related study by Warren (3442) in 1969 attempted to separate and identify caffeine and its metabolites in human blood. A 2-stage system for thin-layer chromatographic separation was devised and applied to blood samples from human volunteers. It appeared that the first step in caffeine metabolism in man is the removal of the 3-methyl group and the formation of 1,7-dimethylxanthine. It was also noted that a much longer time is required to "decaffeinate" habitual coffee drinkers than is true of non-drinkers.

Heyden (1396) published a review in 1969 of information relevant to answering the question: "Does Coffee Influence the Lipid Metabolism?". The review deals with the influence of caffeine on free fatty acids and on cholesterol metabolism as related to atherogenesis. The author tends toward the belief that coffee does temporarily raise the serum free fatty acid level; that questions exist regarding serum lipid and lipoprotein levels influenced by coffee; and that insufficient evidence linking cholesterol levels with coffee intake has been presented.

The influence of caffeine on blood glucose in mice with hereditary-obese hyperglycemic syndrome was reported by Kuftinec and Mayer (1828) in 1964. The mice were given single doses of 2 mg caffeine intravenously, and glucose determinations made at a wide range of intervals of from 3

hours to 60 days. Within 12 hours, the initial blood glucose level of 300 mg/100 ml in the obese mice had nearly doubled, peaking at 600 mg/100 ml in 4 days. Sixty days later, the glucose levels were still about double the initial values. Glucose tolerance tests of obese mice after an intraperitoneal dose of 50 mg glucose following the caffeine treatment, produced negative results, probably due to the already-high blood sugar levels. Insulin tolerance tests were also negative. Coffee treatments produced results similar to above, but the glucose levels in obese mice continued elevated 68 days after coffee withdrawal, falling to very low levels by 90 days, and 18 of the 24 mice treated had died by the 100th day.

The effects of daily caffeine ingestion on the rat liver microsomal enzymes were reported by Khanna and Cornish (1665) in 1973. Male rats were given 20-24 mg/kg caffeine daily in drinking water and were variously sacrificed at 4 to 56 days, liver samples removed and analyzed for enzyme and other factors. Acetanilide hydroxylation and aminopyrine N-demethylation enzyme activities were minimally stimulated after 4 days of treatment. A six-week study of caffeine administration followed by several days of injected sodium phenobarbitone showed that caffeine prevented a response to the drug equal to that of untreated animals. A similar experiment lasting 14 weeks, with a determination of hepatic microsomal levels of cytochrome P_{450} and cytochrome b_5 showed that oral caffeine had no influence on cytochrome levels, but that the additional treatment with phenobarbitone increased the P_{450} levels and decreased b_5 levels significantly.

Zimbardo and Barry (3585) in 1958 observed that a dose of 20 mg intraperitoneally administered caffeine enhanced the sexual activity of male hooded rats.

Rats maintained on low-casein, high-fat diets deficient in choline were given 0.3% caffeine for several weeks (also 0.4 and 0.6% caffeine for about a week in addition, in some instances) and sacrificed. Livers were analyzed for lipotropic activities (liver fat content). Heppel et al. (1377) concluded from this study in 1947, that caffeine possessed lipotropic activity.

Naismith et al. (2299) in 1969 fed rats a starch-based diet free of cholesterol and supplemented variously with tea, coffee or pure caffeine in a study of the influence of caffeine-containing beverages on growth, food utilization and plasma lipids in the rat. After 54 days on the various diets, the only effects of caffeine observed were in the plasma lipid values, cholesterol and phospholipid concentrations, all of which rose, and the triglyceride concentration, which fell.

Heyden et al. (1399) reported in 1969 that experiments with rabbits given atherogenic diets which included cholesterol, and with coffee or caffeine benzoate, failed to demonstrate a relationship between coffee consumption and ischemic heart disease. The doses of caffeine used were 12.5-16.7 mg caffeine daily for 84 days which was comparable to a daily human intake of 9-12 cups of coffee containing 100 mg caffeine per cup. The authors regarded "a single epidemiological observation showing a positive relation between coffee intake and coronary disease" with some skepticism.

Several studies by Roth and Ivy (2718) in 1944 were performed to determine whether caffeine stimulates gastric secretion in man, cat and the dog. Caffeine in doses of 250 mg given to dogs subcutaneously, intramuscularly and intravenously did not result in stimulation of gastric secretion. Oral doses of 65-125 mg caffeine given intravenously or by pyloric intubation to cats provoked marked increase in gastric secretion; 250 mg given by gastric intubation or intramuscularly to human subjects also produced marked stimulation of gastric secretion.

Dose-dependent effects of caffeine given to dogs subcutaneously, intravenously and orally on gastric evacuation, animated peristalsis of the small intestine, and some colonic spasticity were observed by Foti and Egyed (991) in 1953, the caffeine doses varied from 10 to 50 mg/kg.

Scott and Chen (2900) in 1944 tested the diuretic effect of caffeine in dog and in man. Dogs received 10 mg/kg caffeine intravenously; human subjects, 200 mg orally. Both treatments resulted in increased urine output.

The effects of caffeine on free fatty acids and blood coagulation factors of dogs were reported by Bellet et al. (227) in 1968. Caffeine sodium benzoate, 25 mg/kg, was administered intravenously to dogs and several blood samples were taken over a 4-hour period. No influence of caffeine in clotting times were observed, but significant increases in the levels of serum free fatty acids were seen.

Thayer et al. (3218) reported in 1971 the results of in vitro studies of HeLa cell division in caffeine solutions either as suspensions or adherent. Caffeine concentrations of 5-20 micrograms/ml continuously bathed the cells which were periodically examined for chromosome aberrations, particularly chromatid breaks. Neither the growth of the HeLa cultures nor the incidence of chromatid breaks observed were significantly affected by the caffeine, at the levels employed.

The effect of caffeine ingestion on oral glucose tolerance curves in normal human subjects was studied by Feinberg et al. (934) in 1968. A high carbohydrate diet was given to healthy adults for several days, and after a night of fasting, 1 g glucose/kg plus 5 g instant coffee were given orally. Blood samples at intervals were tested for glucose concentrations and in several cases for serum free fatty acids. Serum immunoreactive insulin was also determined. The glucose tolerance curve was significantly altered when 5 g coffee was given with the test meal, but only at 30 and 60 minutes after the test meal. Control and test groups showed no difference in serum free fatty acid concentration until 3 hours after the test meal at which time the group receiving coffee showed a significant increase in free fatty acid. No significant difference was observed in the immunoreactive insulin values due to caffeine.

Bellet et al. (224, 226, 225) tested the effects of coffee and caffeine sodium benzoate on free fatty acid concentrations in humans by oral and intramuscular injection and in dogs by the latter route. The results in both human and animal experiments showed consistent and significant free fatty acid mobilization; the mean serum free fatty acid

levels were markedly increased. A third report on cola drinks given to human subjects indicated the same results, but with a slight difference due to the sugar in the cola drink; an initial drop in the serum free fatty acid levels preceded the anticipated rise, probably due to suppression of the caffeine-induced free fatty acid mobilization by the sucrose through reesterification of the released free fatty acids.

A case history reported by Alberti et al. (45) in 1972, described a patient with diabetes mellitus who had been under treatment for a prolonged period, during which caffeine in doses of up to 7 g/day had been given (equivalent to 50 cups of coffee daily). Six days after withdrawal of the caffeine, tests indicated no change in glucose tolerance, and minimal change in insulin secretion. A moderate fall in serum free fatty acid levels and a marked decrease in circulating ketone bodies were observed.

Urinalyses for adrenaline and noradrenaline in human subjects given caffeine (225 mg) in coffee by Levi (1928) in 1967, showed an increased urinary excretion of both hormones, significantly with respect to adrenaline, less so in noradrenaline. Other factors such as urinary volume, specific gravity and creatinine excretion were not substantially changed.

Avogaro et al. (130) in 1973 investigated the influence of age on caffeine effects in plasma and urine cortisol levels in human subjects, ranging in age from 15 to 70 years, and all accustomed to drinking several or more cups of coffee daily. Periodic blood sample analyses indicated no appreciable change in blood glucose in response to 250 mg caffeine; plasma free fatty acids and cortisol levels were significantly increased; urinary volume and creatinine clearance were relatively unaffected. The free fatty acid and cortisol level increases were more marked among the younger subjects; no other age-dependent differences were noted.

Deakins (709) in 1939, in self-administered tests of coffee and caffeine in large doses (0.5 g), observed a depression in the peak sugar-tolerance curve, with a delayed return of blood glucose to pretreatment levels. Caffeine alone did not raise the blood sugar level appreciably. Cheraskin (568), however, in 1967 gave oral doses of 25 mg caffeine to healthy dental students and observed a significant increase in blood glucose levels.

Bellet et al. (228) in 1968 performed urinalyses on young male human subjects given 220 mg caffeine as instant coffee, testing the effects of coffee ingestion on adrenocortical secretion. Urinary 11-hydroxycorticosteroid (11-OHCS) which include cortisol, 20-hydroxycortisol and corticosterone. A significant increase in urinary excretion of 11-OHCS was observed, indicating caffeine stimulation of adrenocortical activity. Similar treatment of dogs gave results supporting the findings in human subjects.

Experiments on the induction of creatinuria in man by oral administration of at least 1 mg/kg caffeine were described by Bachmann et al. (140) in 1942. No apparent relationship was observed between the size of the

caffeine dose and the amount of creatine excreted nor were total O_2 and CO_2 consumption and elimination related. The increased urinary creatine was associated with an increased protein metabolism rather than with carbohydrate oxidation.

The effects of caffeine ingestion on uric acid excretion in healthy human males were studied by Clark and DeLorimier (598) in 1926. Oral doses of caffeine varying from 250 to 1000 mg/day produced a increased uric acid concentration in both blood and urine; the effect was not dose-related. The initial (8-12 hours) increase in uric acid was followed by a decrease.

Zeller (3572) in 1968, studied the effects of coffee on fat metabolism in healthy subjects and in patients with liver disease. Regular coffee produced an increase in serum free fatty acids; decaffeinated did not, and the caffeine effects were more pronounced in patients with liver diseases than in healthy subjects.

Ruffo (2744) in 1972 proposed a model by which the pharmacological mechanism of drugs on enzyme systems might be explained. Caffeine exerts competitive inhibition on the activity of the phosphodiesterase responsible for the hydrolysis of cyclic AMP in muscle and liver, the increased cyclic AMP starts a series of reactions catalyzed by specific enzymes. Caffeine, thus is shown to be capable of controlling glycogenolysis and the glucidic metabolism. Lipase, responsible for an increase in free fatty acids is also activated by caffeine.

Wachman et al. (3417) in 1970 tested decaffeinated and caffeinated coffees on human subjects to demonstrate the effect of caffeine on blood glucose levels and plasma immuno-reactive insulin values. Caffeine produced an hyperglycemic effect and reduced the insulin response to injected glucose.

Danilov (688) in 1960 conducted chronic experiments on intact, spinal and sympathectomized spinal dogs which indicated that caffeine produced profound changes in reflex activity in the spinal cord. The intensity and duration of the caffeine influence was dose-dependent, lasting 1-2 days after small doses of 3.5-8 mg/kg, and 3-5 days after doses of 20-80 mg/kg orally. Caffeine directly affected the spinal cord centers.

Strubelt et al. (3116) in 1970 investigated the possibility of caffeine exerting an hepatotoxic effect, using rats. Doses of 60 mg/kg given either subcutaneously or intraperitoneally increased serum levels of free fatty acids but no histological evidence was found in liver examinations to warrant a consideration of caffeine as possessing hepatoxic characteristics.

The influence of age on caffeine effects on heart function and metabolism was studied by Ammon and Estler (77) in 1973 using young rats (2 months old) and older rats (15-18 months) given 40 mg/kg caffeine intravenously. Blood pressure and frequency of heart beat were more markedly influenced (increased) in the older animals; ATP and creatinphosphate concentrations in heart muscle were similar in both age groups.

Hughes and Forney (1473) in 1961 performed experiments with various

combinations of alcohol and caffeine on the behavior of rats to test a generalization that caffeine would counteract the effects of overindulgence in alcohol. The animals were conditioned in an avoidance response in special equipment involving warning lights, electric shock and "safe" areas. Drugs were given intraperitoneally; alcohol as 5% solution (dose of 1 g/kg), caffeine as the citrate in doses of 50, 100 or 150 mg/kg. The alcohol alone caused a slight (5%) reduction of the conditioned response; caffeine produced a reduction proportional to the dose. The combination of alcohol-caffeine caused a greater reduction in conditioned response than explicable as a simple sum of the individual effects (synergism). No drug antagonism between caffeine and alcohol was observed.

The presumption based on early experimentation that caffeine reduces digitalis toxicity was tested by Scriabine and Bellet (2906) in 1967, using mongrel dogs, caffeine sodium benzoate and digitalis (as digoxin). The LD_{50} for digoxin was determined to be 0.26 mg/kg; dogs pretreated with 50 mg/kg caffeine intramuscularly, showed an LD_{50} of 0.27 mg/kg; intravenous caffeine of 100 mg/kg dosage prior to digoxin infusion did not significantly alter the lethal dose-range of digoxin in controls. No antagonism of digitalis toxicity by caffeine was demonstrated.

Caffeine and dexedrine were studied as possible antagonists to alcohol by Newman and Newman (2346) in 1956. Human volunteers were given about 180 mg/kg ethanol (12-13 g) at 45 minutes after ingesting dexedrine, 15 mg or caffeine, 300 mg. Tests of the nervous system function, such as an equilibrium test, balancing on one foot with eyes closed; hand steadiness, etc. were used to assess the depressant effect of alcohol versus the stimulating influence of dexedrine and caffeine. Nc drug antagonism was observed in these experiments.

Mitoma et al. (2207) in 1969 used Sprague-Dawley rats in experiments demonstrating the stimulant action of caffeine on drug metabolism; the effects of caffeine were compared with those of phenobarbital. The drugs were given twice daily for 4.5 days; phenobarbital intraperitoneally 38 mg/kg, caffeine, orally 75 mg/kg. After sacrifice, livers were removed and assayed; both drugs stimulated hydroxylase and N-demethylase activities, but increased liver weight and microsomal protein or CO-binding pigment content in the liver were seen only in the phenobarbital treatment. Caffeine acted primarily, if not exclusively, on the microsomal fraction of the liver. When acetanilide was the substrate, the two drugs acted additively as stimulants. An earlier paper by Mitoma et al. (2206) in 1968 presented similar studies with caffeine alone as a microsomal inducer. The minimum caffeine dose which elicited the liver microsomal interaction was 40 mg/kg; an equivalent to about 35 cups of coffee per day for a 70 kg man on a straight weight basis; or about 8 cups daily on the basis of metabolic weight. The authors speculated that moderate coffee drinking in man could have an inducing effect on the liver drug-metabolizing system.

Studies by Epstein et al. (884) in 1970 on mutagenicity included experiments designed to test the possibility of caffeine potentiation of known mutagens, such as methylmethanesulfonate, TEPA and x-rays. Doses of caffeine given to male mice intraperitoneally ranged from 168 to 200 mg/kg, given orally, 200 to 1600 mg/kg/day, combined with the mutagens. On the basis of fetal deaths from matings of treated males with untreated, virgin females, no synergistic effect of caffeine with the mutagens was observed.

Haldi et al. (1287) in 1947, in studies demonstrating the modification of the stimulating effect of caffeine, observed that 1500 mg/kg sucrose given simultaneously with 75 mg/kg caffeine orally by stomach tube to rats reduced the spontaneous increase in activity induced by caffeine alone. Peptone and vegetable oil as vehicles for the caffeine produced similar effects.

CAFFEINE

Chemical Information

I. Nomenclature

A. Common Names

1. Coffeine
2. Caffeine
3. Thein
4. Guaranine
5. Methyltheobromine

B. Chemical Names

1. Caffeine
2. 1,3,7-Trimethylxanthine
3. 1,3,7-Trimethyl-2,6-dioxopurine

C. Trade Name

No-Doz

D. Chemical Abstracts Registry Number

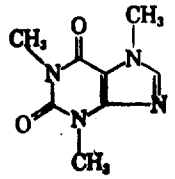
000058-08-2

II. Empirical Formula

$C_8H_{10}N_4O_2$

III. Structural Formula

1,3,7-Trimethylxanthine



IV. Molecular Weight

194.19

V. Specifications

From Food Chemicals Codex:

Assay	Not less than 98.5% and not more than the equivalent of 101.0% of $C_8H_{10}N_4O_2$, calculated on the anhydrous basis
Melting range	Between 235 degrees and 237.5 degrees
Water	Anhydrous caffeine, not more than 0.5%; hydrous caffeine, not more than 8.5%
Limits of impurities	
Arsenic (as As)	Not more than 3 ppm (0.003%)
Heavy metals (as Pb)	Not more than 20 ppm (0.002%)
Lead	Not more than 10 ppm (0.001%)
Readily carbonizable substances	Passes test
Residue on ignition	Not more than 0.1%

VI. Description

A. General Characteristics

Anhydrous hexagonal prisms by sublimation; monohydrate white powder or white, felted crystals. Odorless, with bitter taste.

B. Physical Properties

Caffeine solutions are neutral to litmus. The hydrate is efflorescent in air. One gram soluble in 46 ml water, 66 ml alcohol, 5.5 ml chloroform, 530 ml ether and 100 ml benzene.

C. Stability

Store anhydrous caffeine in well-closed containers; hydrous caffeine should be stored in tight containers.

VII. Analytical Methods

Chemical and microchemical tests for caffeine may be found in Official Methods of Analysis, AOAC (3603) sections 8.032-8.039; 14.019-14.024; and 32.291-32.294.

Borker and Sloman (363) recommended in 1965 that a spectral-chromatographic modified form of the Levine procedure be considered as a replacement or alternative for the method described in the AOAC sections 8.032-8.036. The original Levine method used an acid extraction medium; the modification substitutes a basic extraction medium. The modified Levine technique is as follows:

Spectral-Chromatographic Determination
of Caffeine

(Applicable to decaffeinated coffee)

Preparation of Samples

Grind green and roasted coffees to about 50-70 mesh. Use good coffee grinder or large Waring Blendor, and keep sample cold with Dry Ice while grinding to avoid pastiness.

Place 1.0 g ground decaffeinated coffee or 0.5 g decaffeinated sol. coffee in 100 ml beaker. Add 5 ml NH_4OH (1 + 2) and heat 2 min. on steam bath. Add 6 g Celite 545 and mix thoroly.

Preparation of Column

(a) Acid column. -- Place fine glass wool plug in base of 25 X 250 mm column. Add 2 ml 4N H_2SO_4 to 2.0 g Celite 545 and mix well by kneading with spatula blade. Transfer to column, using powder funnel, and tamp, using gentle pressure, to uniform mass. Place small glass wool wad above surface. Insert tip into 50 ml vol. flask.

(b) Basic column. -- Layer A. -- Mix 3 g Celite 545 and 2 ml 2N NaOH, and place in 25 X 250 mm column over glass wool plug as above. Layer B. -- Transfer sample plus Celite mixt. to column directly over layer A. Dry-wash beaker with ca 1 g dry Celite, transfer to column, and tamp to uniform mass.

(Both acid Celite and basic Celite mixts may be prepd in large batches and used as needed. In this case, use 4.2 g acid mixt. and 5 g base mixt./column.)

Determination

Mount basic column above acid column. Pass 150 ml H_2O-satd ether thru basic column to acid column. Then pass 50 ml ether thru acid column. Place 50 ml vol. flask under acid column. Pass 50 ml H_2O-satd $CHCl_3$ over acid column, washing tip of basic column with first portion. Dil. contents of vol. flask to 50 ml with H_2O-satd $CHCl_3$, mix, and read absorbance at 276 mu against $CHCl_3$ blank.

Prep. caffeine stds contg 0.25, 0.5, and 0.75 mg/50 ml in H_2O-satd $CHCl_3$. Establish absorptivity of stds for spectrophotometer used, and check occasionally. Calc. caffeine in samples from absorptivity of stds.

A subsequent report by Johnson (1566) of the FDA indicates that the foregoing modified Levine technique was adopted by the A.O.A.C. as official. The technique is described again. Grab and Runstein (1173) presented a method for the determination of caffeine in blood plasma. The gas chromatographic method is described as follows:

EXPERIMENTAL

Equipment—A Varian Aerograph series 1200 gas chromatograph with a flame-ionization detector and a Varian model 20 recorder set at 20 in. hr.$^{-1}$ was used. The column employed was a 1.9 m. (6 ft.) stainless steel helix, 0.32 cm. (1/8 in.) o.d. packed with 3% OV 17 on Chromosorb W 100–120 mesh AW/-DMCS H.P. (Applied Science lot 4223). The N_2 gas flow rate was 30 ml./min. Operating temperatures were: oven, 200°; injection port, 260°; and detector, 260°. Attenuations from 0.1 × 8 to 0.1 × 64 were used.

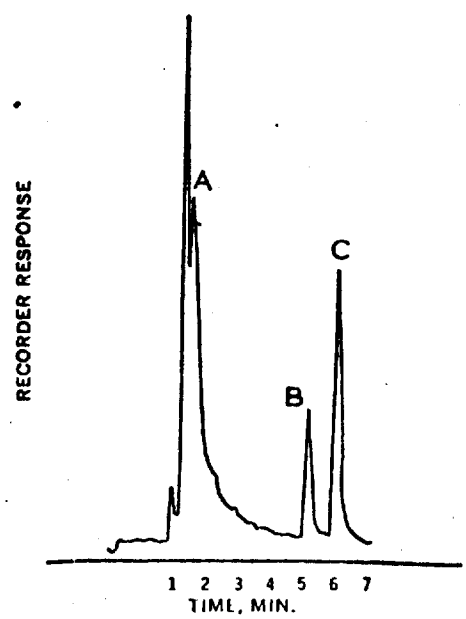


Fig. 1—Typical chromatogram. Key: A, carbon disulfide; B, hexobarbital (R_t = 4.3); *C, caffeine* (R_t = 5.2). *Column 3% OV 17.*

Reagents—(*a*) Caffeine (Eastman Organic) purified by vacuum sublimation; (*b*) hexobarbital (Winthrop), the internal standard; (*c*) reagent grade carbon disulfide (MCB) further purified by distillation; (*d*) heparin solution, 1,000 units/ml. (free of preservatives); (*e*) 2.5 *N* sodium hydroxide (Fisher Certified Reagent); (*f*) technical grade chloroform (Baker) freshly distilled.

Standard Curve—Standard curves were obtained by preparing solutions of caffeine 0.75–6.0 mcg./100 µl. and hexobarbital 2.0 mcg./100 µl. in carbon disulfide (20). Both caffeine and hexobarbital give sharp peaks with some slight tailing (Fig. 1). The standard curve given by the peak-height ratio of caffeine/hexobarbital *versus* caffeine concentration was linear and reproducible (Fig. 2).

Preparation of Plasma Samples—A 5-ml. sample of blood was taken, added to 2 drops of heparin, and spun down in a centrifuge (IEC International Clinical Centrifuge) for 10 min. at 2500–3000 r.p.m. Two milliliters of plasma was pipeted into a 25-ml. round-bottom screw-cap Pyrex tube with a Teflon-lined cap. The pH was adjusted to 11.5–12.0 with 2.5 *N* sodium hydroxide. To this 10 ml. of chloroform was added. The tubes were then agitated for 15 min. and then centrifuged (IEC International Centrifuge series 2) for 10 min. at 1,000 r.p.m. Using a 10-ml. hypodermic syringe with a 10-cm (4 in.) cannula, 75% of the chloroform layer was withdrawn and placed into a conical ground-glass stoppered 15-ml. centrifuge tube. The chloroform extract was then evaporated to dryness in a 60–80° water bath, mounted on a steam cone. Bumping was prevented by placing an antibumping chip, previously boiled in carbon disulfide, into the tube, just prior to driving off the chloroform. One milliliter of hexobarbital solution (2 mcg./ml.) in carbon disulfide was pipeted into the tube. This solution was then concentrated to approximately 100 µl. by heating in the water bath at 40–60°. A 2-µl. sample of this concentrate was then injected onto the column.

Kramarenko and Akopyan (1781) have described a photoelectrocolorimetric method for caffeine determination.

VIII. Occurrence

Seeds from the fruit of plants of several families, the chocolate family, Theobroma and Coffea from the madder family provide cacao (cocoa and chocolate), Kola nut and coffee; leaves and other plant parts of the tea family, Theaceae, principally Camellia sinensis, and of the Ilex, provide tea and mate. Beverages including the "soft drinks" or "colas" made from these plant parts the world over all contain caffeine which is probably the most widely consumed drug (stimulant). The Code of Federal Regulations, January 1968, Title 21, Chapter 1, Subpart B, Paragraph 121.101, lists caffeine as GRAS with a tolerance of 0.02% in cola-type beverages.

CAFFEINE

Biological Data

I. Acute Toxicity

Table I is derived from the literature which is abstracted in this section; Table II is taken from the Handbook of Toxicology, Volume I., Edited by William G. Spector (1956) pages 56-57:

Table I.

Substance	Animal	Sex & No.	Route	Dosage (mg/kg	Measurement	Ref.
Caffeine	Mouse	20 M	i.p.	277	LD_{50}	2264
Caffeine	Mouse	28	p.o. (lean)	400	LD_{50}	1828
Caffeine	Mouse	42	p.o. (obese)	80	LD_{50}	1828
Caffeine	Mouse	30	i.v.	72-86	LD_{50}	2902
Caffeine (Synthetic)	Mouse	30	i.v.	70-80	LD_{50}	2902
Caffeine	Mouse	6	i.p.	525	LD_{50}	2116
Caffeine	Mouse	6	p.o.	878	LD_{50}	2116
Caffeine	Mouse	5 F	i.v. (non preg.)	89.2	LD_{50}	222
Caffeine	Mouse	5 F	i.v. (preg.)	96.3	LD_{50}	222
Caffeine	Rat	16	i.p. (1.5 mo. age)	200	LD_{50}	2528
Caffeine	Rat	10	i.p. (2-4 mo. age)	205	LD_{50}	2528
Caffeine	Rat	20	i.p. (old age)	167	LD_{50}	2528
Caffeine	Rat	40 F	p.o. (fasted)	174-210	LD_{50}	389
Caffeine	Rat	50 F	p.o. (fed)	254-274	LD_{50}	394
Caffeine	Guinea pig	? M	p.o. (fasted)	209-251	LD_{50}	390
Caffeine	Dog	?	p.o. (15lb. 4 mo)	3250	LD_{50}	3485
Caffeine	Man	1 M	i.v. (patient)	3200	LD_{50}	1571
Caffeine	Man	1 M	p.o.	19,000	LD_{50}	1669

Table II

Compound	Animal	Route	Dose	Dosage mg/kg	Time of Death	Reference
Caffeine	Frog	sc	LD	120-130	4-5 da	Fühner, Arch. exp. Path. Pharm. 166:455, 1932.
	Mouse	sc	LD	180-190	2-3 da	Ibid
	Mouse	ip	MLD	220		Flury, Abderhalden's Hdb. 4.7b:1336.
	Mouse	ip	LD	500		Rpt. Chemother. Leukemia, So. Res. Inst. Aug. 1945
	Mouse	ip	LD	250		Ibid
	Mouse	iv	LD_{50}	100.9±6.67		Scott, J. Pharm. Exp. Ther. 82:89, 1944.
	Rat	or	LD_{50}	200		Smith, J. Pharm. Exp. Ther. 55:200, 1935.
	Rat	or	LD_{50}	233±14		Scott, J. Pharm. Exp. Ther. 82:89, 1944.
	Rat	sc	LD	70-130		Flury, Abderhalden's Hdb. 4.7b:1336.
	Rat	sc	LD	250	2 hr	Kreitmair, Arch. exp. Path. Pharm. 87:607, 1937.
	Rat	ip	MLD	210-280		Flury, Abderhalden's Hdb. 4.7b:1335.
	Rat	iv	LD_{50}	104.8±1.87		Scott, J. Pharm. Exp. Ther. 82:89, 1944.
	Guinea pig	sc	MLD	200-240		Flury, Abderhalden's Hdb. 4.7b:1335.
	Guinea pig	ip	MLD	220-250		Ibid
	Rabbit	or	MLD	290-350		Ibid
	Rabbit	or	LD	350-360		Salant, J. Pharm. Exp. Ther. 1:572, 1910.
	Rabbit	sc	MLD	200-300		Flury, Abderhalden's Hdb. 4.7b:1335.
	Rabbit	sc	LD	270-280	1-4 hr	Salant, J. Pharm. Exp. Ther. 1:572, 1910.
	Rabbit	im	LD	200	4 hr	Ibid
	Rabbit	iv	LD	80-100		Flury, Abderhalden's Hdb. 4.7b:1335.
	Cat	or	MLD	100-150		Ibid
	Cat	sc	MLD	150		Ibid
	Cat	sc	LD	150-155	1 hr±	Salant, J. Pharm. Exp. Ther. 1:572, 1910.
	Cat	ip	MLD	180-200		Flury, Abderhalden's Hdb. 4.7b:1335.
	Cat	iv	MLD	80-100		Ibid
	Dog	or	MLD	140-150		Ibid
	Dog	sc	MLD	500		Ibid
	Dog	sc	LD	110	Few hr	Salant, J. Pharm. Exp. Ther. 1:572, 1910.
	Dog	iv	LD_{50}*	175		Pilcher, J. Pharm. Exp. Ther. 3:19, 1911-12.
	Cat	iv	LD	175		Sollmann, J. Pharm. Exp. Ther. 3:19, 1911-12.

Mice

The influence of various genetic and environmental factors on the response to drug toxicity has been the subject of numerous studies; Muller and Vernikos-Danellis (2264) in 1970 investigated the effects of mild environmental temperature changes and dehydration on the toxicity of the stimulants, caffeine and dextroamphetamine. Male Swiss-Webster mice weighing 25-30 g were used, 20 mice for each drug dose level. Twenty-four-hour LD_{50}'s were selected for temperature variations; dehydration studies were followed until 100% mortalities were recorded. The normal environmental temperature was 22 degrees C; temperature studies of drug toxicity were made at 15 degrees C and at 30 degrees C. Exposures to the experimental temperatures were for either 1 hour or 3 days before injection of the drug, and were maintained throughout the studies. Dehydration studies consisted of pre-injection withdrawal of water for 3 days and postinjection for 5 days. Body temperatures of the animals were monitored and varied less than a degree during 15, 22 and 30 degrees C environmental temperatures. Five groups of 20 animals each were treated to produce the LD_{50}'s.

The LD_{50}'s for caffeine after 1 hour and 3-day preinjection exposures to 15 and 30 degrees C compared to 22 degrees are shown in the following figure:

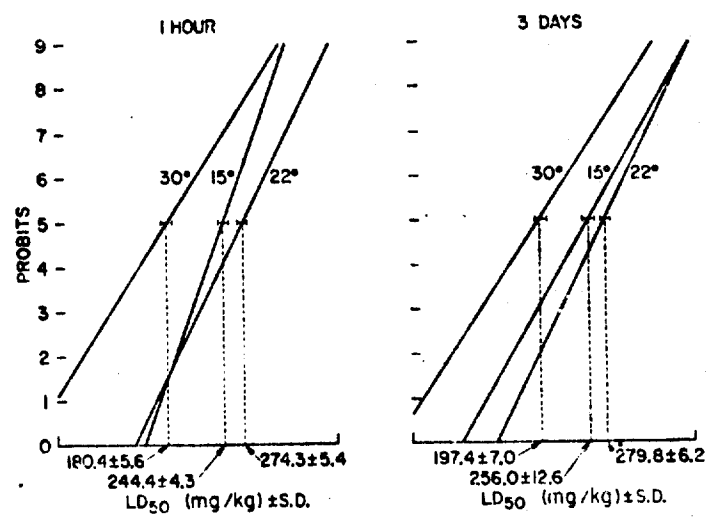


FIG. 2. LD50's of caffeine at three temperatures after one-hour and three-day preinjection exposure periods.

Both warming and cooling before injection of caffeine increased the toxicity, but significantly so only at 30 degrees; no significant difference was observed due to the preinjection periods of 1 hour or 3 days. The dehydration studies showed LD_{50}'s for caffeine slightly reduced from controls at 22 degrees C, little more at 15 degrees C but 3-fold greater at 30 degrees C. Combining the stresses of temperature changes and dehydration in mice exposed to cold and dehydration results in an additive influence on caffeine toxicity; combined heat and dehydration increased the toxicity of caffeine far in excess of an additive predicted value. It appears to be a clear potentiation of the two adverse environmental factors.

The authors suggested, after some discussion of the probable mechanisms by which stress-drug interaction may be explained, concluded that their studies indicated that the alteration of drug toxicity is related to kind of environmental change involved and the action mechanism of the drug itself. When several stressful stimuli are combined, the effect on drug toxicity is not entirely predictable.

Mice with hereditary obese hyperglycemic syndrome, a recessive character, were shown by Kuftinec and Mayer (1828) to be much more sensitive to caffeine toxicity than normal animals. The report gives no details of experiments, but only results. The LD_{50} (oral dose ?) for 28 nonobese lean mice was found to be 400 mg/kg; for 42 obese hyperglycemic animals, the LD_{50} was 80 mg/kg. The effects of treating fasted animals with caffeine by injection (intravenous ?) and noting survival produced the following results: 2 mg caffeine per (obese) mouse after 24 hours of fasting showed 18 of 25 injected animals surviving (72%), but with 48 hours of fasting, only 2 of 20 animals or 10%, survived; all lean mice given the same treatment but with doses of 5 mg caffeine per animal survived.

The remainder of the study will be found in the Biochemistry IV Section of this monograph.

Scott et al. (2902) reported in 1947 the comparative results of synthetic and commercial caffeine given intravenously to 30 mice each for the two caffeines in the determination of LD_{50}'s. The LD_{50} of synthetic caffeine was determined to be 75.51 plus or minus 5.39 mg/kg; the LD_{50} for commercial caffeine was 79.36 plus or minus 6.94 mg/kg. The difference was not statistically significant. The central stimulation action of the synthetic and commercial caffeines was also indistinguishable.

The acute toxic and emetic properties of a number of methylated xanthines and congeners used therapeutically as diuretics and bronchodilators were determined by McColl et al. (2116) in 1956. The toxicity studies used white mice of both sexes, weighing 18-22 g; the emetic studies employed dogs and cats. (Only the acute toxicity experiments are reviewed in this section.)

LD_{50}'s were estimated from data acquired by using 6 animals at each dose level and 3-5 dose levels per day. Deaths which occurred within one week of treatment were included in the LD_{50} data; in the case of caffeine, all deaths occurred within 24 hours. The caffeine was administered as the sodium benzoate, intraperitoneally and orally. The following tables show the drugs and toxicities for the series tested:

TABLE 1

Acute intraperitoneal toxicity in mice

Xanthine	LD_{50}	95% Fiducial Limits	Slope
	mgm./kgm.	*mgm./kgm.*	
1-Allyl theobromine	102	79–130	6.5
7-Isoamyl theophylline†	211	203–221	6.9
Theophylline	217	208–225	34.7
1-Isoamyl theobromine†	222	203–243	8.9
7-Benzyl theophylline*	228	199–319	13.7
1-Butyl theobromine†	230	204–260	11.9
7-Diethylaminoethyl theophylline	254	234–275	18.9
Aminophylline	257	247–268	15.9
7-Butyl theophylline†	272	236–319	8.9
7-Chloroethyl theophylline	281	264–299	15.4
7-Allyl theophylline	299	273–327	16.1
Caffeine and sodium benzoate	525	481–574	17.5
7-Hydroxyethyl theophylline	599	527–681	11.3
Theobromine sodium acetate	789	712–874	14.0
7-Acetic acid theophylline‡	1180	903–1565	5.1
7-β-Methoxy-γ-hydroxypropyl theophylline	1488	1203–1840	7.0
7-β-γ-Dihydroxypropyl theophylline	1770	1750–1807	8.2

* In corn oil.

† In 25 per cent propylene glycol solution.

‡ In 0.2 *M* sodium acetate (pH 4.6) solution.

TABLE 2

Acute oral toxicity in mice

Xanthine	LD_{50}	95% Fiducial Limits	Slope
	mgm./kgm.	*mgm./kgm.*	
1-Allyl theobromine	191	177–207	18.8
7-Allyl theophylline	315	279–356	11.4
Theophylline	332	270–408	14.0
7-Chloroethyl theophylline	374	343–381	18.4
Theophylline ethylenediamine	391	276–441	4.4
7-Butyl theophylline*	617	427–708	7.7
1-Butyl theobromine*	667	632–695	26.8
7-Isoamyl theophylline*	723	504–1038	4.9
1-Isoamyl theobromine*	772	694–826	13.3
7-Hydroxyethyl theophylline	855	823–887	3.6
Caffeine and sodium benzoate	878	736–1047	8.8
7-Diethylaminoethyl theophylline	1237	1139–1344	17.8
Theobromine sodium acetate	1356	1124–1862	6.2
7-β-Methoxy-γ-hydroxypropyl theophylline	1681	1490–1895	11.2
7-β-γ-Dihydroxypropyl theophylline	1954	1497–2251	5.9
7-Acetic acid theophylline†	2733	1733–4310	2.2

* In 25 per cent propylene glycol solution.

† In 0.2 *M* sodium acetate (pH 4.6) solution.

The emetic activity for each of the xanthines was determined in dogs and cats (not described) by giving half the oral LD_{50} (mg/kg) dose for mice, in gelatin capsules, and reducing the dose until no emesis was observed. The results are shown in the following table, which also includes the oral LD_{50}'s for mice:

TABLE 3

Comparative emetic actions of xanthines in dogs and cats

Xanthine	I Oral Mouse LD_{50}	II Dog ED_{50}	III Cat ED_{50}	IV Dog Emetic Index	V Cat Emetic Index
		mgm./kgm.	*mgm./kgm.*		
7-Hydroxyethyl theophylline	855	380	110	0.45	0.13
1-Allyl theobromine	191	73	—	0.38	—
8-Chlorotheophylline	440*	165	82	0.38	0.19
Theophylline	332	120	120	0.36	0.36
Theophylline ethylenediamine	391	140	100	0.36	0.26
7-Butyl theophylline	617	210	60	0.34	0.10
7-Chloroethyl theophylline	374	112	70	0.30	0.19
7-Allyl theophylline	315	80	80	0.25	0.25
Theobromine sodium acetate	1356	338	—	0.25	—
Caffeine and sodium benzoate	878	215	—	0.25	—
7-Diethylaminoethyl theophylline	1237	300	210	0.24	0.18
7-β-Methoxy-γ-hydroxypropyl theophylline	1681	400	300	0.24	0.18
7-β-γ-Dihydroxypropyl theophylline	1954	375–750	94–187	0.2–0.3	0.05–0.1
7-Isoamyl theophylline	723	105	80	0.15	0.11
1-Isoamyl theobromine	772	100	100	0.13	0.13
7-Acetic acid theophylline	2733	350	300	0.13	0.11
1-Butyl theobromine	667	43	43	0.06	0.06

* LD_{50} value taken from DeJongh *et al.* (1951).

The influence of pregnancy on the acute toxicity of various compounds, including caffeine, was reported by Belilles (222) in 1972. Pregnant adult female Charles River CD-1 mice and nonpregnant adult female mice of the same strain were given graded doses of test materials. Five mice per dose level and at least 4 different dose levels were employed. Treatment was administered on the 13th day of gestation; 3 days later cesarean sections were performed and uterine contents inspected. Pregnant mice that died were necropsied, and nonpregnant mice were sacrificed after 7 days. Caffeine solutions in distilled water were administered intravenously; the LD_{50} for caffeine in nonpregnant mice was determined to be 89.2 mg/kg (95% confidence limits, 68.4-116 mg/kg); for pregnant mice, the LD_{50} was 96.3 mg/kg (95% confidence limits, 79.8-116 mg/kg). The differences were not significant.

Rats

Poe and Johnson (2528) in 1953 investigated the toxicity of caffeine,

theobromine and theophylline given to white rats and microorganisms. Only the caffeine and rat studies will be considered in this monograph. Methods and experimental details were not included in this report by the authors, having been given in earlier reports. The determination of LD_{50}'s by intraperitoneal injection and the relationship of caffeine toxicity to the age of treated animals gave results shown in the following tables:

Table 1.

Toxicity of Caffeine to White Rats, Age 1½ Months by Intraperitoneal Injection

Dose Alkaloid mg/kg	pH of Solution	Number Rats Injected	Number of Deaths	Per Cent Mortality	Av. Time to Death Hrs.	Av. Time to Death Mins.	Deaths after Convulsions	Survivors of Convulsions	Av. Time to first Convulsions (Minute)
100	3.3	10	0	0					
150	3.3	10	3	30	19	59	1	0	8
200	3.3	16	8	50	16	25	5	8	4
210	3.2	20	15	75	11	51	9	0	9
225	3.4	20	18	90	15	55	13	0	4
250	3.2	10	10	100	11	15	9	0	4
275	3.2	13	13	100	2	48	7	0	3

Table 3.

Comparative Toxicity to white Rats of Different Ages of Caffeine by Intraperitoneal Injection

Dose Alkaloid mg/kg	Young Rats (2 to 4 Months) Number Injected	Young Rats Number Deaths	Young Rats Percent Mortality	Old Rats Number Injected	Old Rats Number Deaths	Old Rats Percent Mortality
100	5	0	0	5	0	0
150	8	2	25	10	4	40
175				20	11	55
200	10	4	40	16	12	75
210	10	6	60	10	9	90
225	10	8	80	10	10	100
250	10	10	100	6	6	100
300	13	13	100			

From dose-mortality curves, the LD_{50} for caffeine was estimated at 200 mg/kg for rats 1.5 months old; 205 mg/kg for rats 2-4 months old; and 167 mg/kg for old rats. Toxic reactions of the caffeine-treated animals were first nervousness, followed by tetanic convulsions within about 4 minutes after injection. Bacteriological studies of the effects of the three alkaloids were reported: caffeine and theophylline inhibited growth and gas production of Escherichia sp. and Aerobacter sp. at levels of about 4-5 mg/ml solutions. Theobromine in concentrations as great as 67 mg/ml solution was ineffective.

Boyd (389) in 1959 reported a study of the clinical and pathological signs of poisoning in rats by caffeine from doses in the range of the oral LD_{50}. Female albino rats, for 16 hours were given caffeine BP, USP in distilled water by stomach tube in a volume of 2 ml/kg body weight. The doses and number of animals per dose were: 0.000 mg/kg (20); 160 mg/kg (8); 180 mg/kg (16); 200 mg/kg (8); and 220 mg/kg (8). Body weights of the rats averaged 203 plus or minus 28 g, and the ages ranged from 3 to 6 months.

Of the 40 treated animals, 19 survived and 21 died; the time to death averaged 30 plus or minus 9.6 hours after treatment. The LD_{50} was calculated to be 192 plus or minus 18 mg/kg.

Clinical signs in those animals which recovered included weakness, tenseness and little inclination to move about; by 6 hours after treatment half the animals showed varying degrees of catalepsis; at 12 hours, eyelids were swollen and inflamed; at 24 hours anorexa and diarrhea, and several showed tremors, pallor and moderate excitement; at 48 hours, half the animals were normal, several were excited and several suffered clonic convulsions lasting a few seconds; at 72 hours all animals had a normal clinical appearance.

Those animals which did not survive showed clinical symptoms in the beginning similar to those of the survivors, but from the 10th hour until death, the deterioration was progressive. Marked anorexia, diarrhea and loss of body weight were seen; anuresis and lowered body temperature led to either tetanic convulsions and respiratory failure or to cardiovascular collapse and death.

Autopsy revealed evidence of fulminating gastroenteritis, lung congestion, hepatitis and nephritis; many organs showed abnormalities due to the toxic effects of caffeine, both of gross appearance and in histopathology.

Boyd et al. (394) reported in 1965 on the chronic oral toxicity of caffeine in rats; the acute oral LD_{50} was first determined and is briefly noted in this section of the monograph. (The main report is abstracted in the following section on short-term studies). Female CBL Wistar albino rats of 150-200 g body weight and no starved were used in the experiments. Five separate doses of caffeine dissolved in water to 20 ml/kg solutions in strengths of 200-350 mg/kg caffeine were given intragastrically to 10 rats each dose and observed for 5 days after treatment. The acute LD_{50} for unstarved rats given caffeine orally was estimated to be 264 plus or minus 10 mg/kg.

Guinea Pigs

In 1960, Boyd (390) reported a study of the separate and combined toxic effects of the ingredients of APC tablets (acetylsalicylic acid, phenacetin and caffeine) in guinea pigs. Young male CBL guinea pigs, weighing 300-500 g were used in the experiments. Only the results with caffeine, and some clinical and pathological comparisons with the other two drugs will be reviewed here). The animals were fasted for 16 hours before given the drug by gastric cannula. The LD_{50} for caffeine in guinea pigs was estimated to be 230 plus or minus 21 mg/kg. The clinical and pathological syndrome was similar to that described for albino rats by Boyd (preceding report); the common cause of death was respiratory failure following tonic-clonic convulsions. Clinical and pathological comparative data for the three APC drugs are shown in the following table:

TABLE 3

A COMPARISON OF CLINICAL AND PATHOLOGICAL SIGNS IN GUINEA PIGS DYING FROM ADMINISTRATION OF ASA, PHENACETIN, CAFFEINE, AND APC

Observation	Acetylsalicylic acid	Phenacetin	Caffeine	APC
$LD_{50} \pm SE$ (g/kg)	1.19 ± 0.073	1.87 ± 0.074	0.230 ± 0.021	1.33 ± 0.040
Early (< 12 hr) deaths (% of total deaths)	81	28	37	50
Delayed (2 days) deaths (% of total deaths)	12	33	29	19
Premortem signs	Convulsions, mania	Hypothermia, stupor	Convulsions, stupor	Hypothermia, stupor, mania
Histopathology:				
1. G.I. Tract	Inflammation	Inflammation	Inflammation	Inflammation
2. Liver	Congestion	Degeneration	Edema	Degeneration
3. Kidneys	Necrosis	Minor	Minor	Edema
4. Heart	Minor	Minor	Congestion	Minor
5. Lungs	Edema	Edema	Edema	Edema
6. Spleen	Contraction	Minor	Congestion	Contraction
7. Adrenals	Congestion	Congestion	Congestion	Congestion
8. Pancreas	Minor	Congestion	Minor	Minor
9. Testes	Minor	Minor	Minor	Minor

Dog

A brief case report by Wigderson (3485) in 1956 described the poisoning of a 15 pound, 4 month old dog that had ingested some caffeine tablets totaling about 3.25 g caffeine. The animal collapsed several hours later in a semitetanic state, was given 3 ml sodium pentobarbital intraperitoneally, but died before further remedies could be undertaken.

Man

Until 10-15 years ago, no deaths attributed to caffeine poisoning had been reported; cases of severe poisoning had, however, been reported. Jokela and Vartiainen (1571) reported in 1959 from the University of Helsinki several hospital cases, one of whom died due to the inadvertent administration of intravenous caffeine-sodium benzoate solution in the place of what was mistakenly assumed to be glucose. Both patients were in therapy for insulin treatment; the one patient, given in rapid succession, 2-20 ml injections containing an estimated 3.2 g caffeine immediately underwent convulsions and died shortly thereafter. The second patient received only 5 ml of the solution or about 0.4 g pure caffeine, and had violent convulsions, whereupon the error of using the caffeine solution in place of glucose was discovered. The patient was than given glucose and revived normally. This event occurred in a Helsinki mental hospital in 1951.

A rare case of death by caffeine poisoning in a 47 year old woman was reported by Khodasevich (1669) in 1957 in Latvia. The woman had been treating herself with caffeine in small doses for "shortness of breath"; on the day of her death, she took by mistake about 250 ml of a 20% caffeine-sodium benzoate solution (about 19 g pure caffeine) and after vomiting and diarrhea, she expired in 30 minutes.

A general, brief-discussion of caffeine toxicity in humans is included in the report; ingestion of caffeine in doses exceeding 1 g produces symptoms of great agitation, hallucination, confused thought, vertigo, fever, tremor in the extremities, convulsions, extreme headache, increased pulse and respiration, vomiting, diarrhea, and a decline in heart activity. Recovery, however, is usually rapid and complete in several days. It is suggested that the human fatal dose of pure caffeine is about 10 g.

II. Short-Term Studies

Rat

During a reproduction study in 1946, Bachmann et al. (141) found no growth retardation in weanling rats of both sexes when 20 of the test animals consumed an average of 40-50 mg/kg/day caffeine in a sweetened beverage which was their only source of liquid. Controls (litter mates of the tests) were given plain tap water - they consumed 30 ml/day. The solid food consisted of Purina Dog Chow supplemented with green food and cod liver oil ad. lib. The 10 test males and 10 control males were weighed weekly for 26 weeks; the females (10 tests and 10 controls) were weighed

weekly for 11 weeks. The data is summarized in Figure 1.

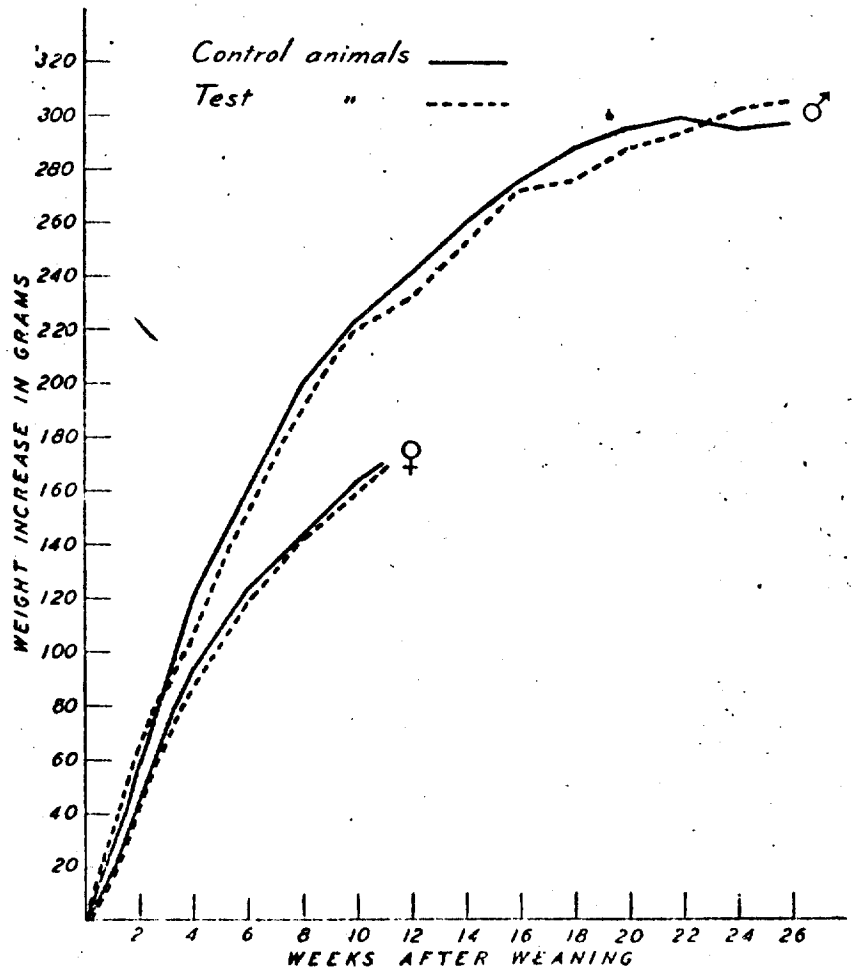


Fig. 1 Growth curves of albino rats on a caffeine containing beverage as their sole fluid intake, as compared with their litter mate controls on water.

A number of experiments have indicated that underweight and poor health generally increase susceptibility to drug toxicity. Peters (2492) in 1966 studied the influence of partial starvation in rats on the toxicity of caffeine. Adult female Wistar albino rats were first placed on diets of food and water ad libitum and daily clinical measurements of food intake, body weight, and urinary pH, protein and glucose concentrations were made. The animals were divided into 8 groups of varying numbers and given a variety of treatments, among which some received daily intragastric doses of 185 mg/kg caffeine as the alkaloid monohydrate USP in 20 ml distilled water. Treatments and other data including mortality rates are summarized in the following table:

TABLE 1

GROUPS, NUMBER PER GROUP, INITIAL BODY WEIGHT, AND TREATMENT OF RATS GIVEN REDUCED FOOD INTAKE AND CAFFEINE, AND THEIR MORTALITY RATES

Group number	Number of animals	Initial body weight[a] (g)	Treatment	Food intake[b] (%)	Mortality %	Mortality: Time to 50% mortality (days)
1	10	185 ± 10	Chow ad libitum + distilled water	100 (14.1 ± 0.7)[d]	0	—
2	9	177 ± 13	Chow ad libitum + caffeine[c]	104 (14.6 ± 2.7)[d]	0	—
3	8	198 ± 12	8 g chow daily + distilled water	57	0	—
4	10	191 ± 18	8 g chow daily + caffeine[c]	57	0	—
5	6	195 ± 10	6 g chow daily + distilled water	43	0	—
6	8	198 ± 14	6 g chow daily + caffeine[c]	43	88	12
7	9	194 ± 14	4 g chow daily + distilled water	28	11	—
8	10	196 ± 19	4 g chow daily + caffeine[c]	28	100	7

[a] Mean ± SD.
[b] As percentage of controls.
[c] Caffeine was administered orally in a dose of 185 mg/kg/day.
[d] Expressed as mean ± SD of mean daily food intake in grams.

Caffeine treatments were begun after one control day on reduced food intake without caffeine. The experiments were terminated at 14 days, after which survivors were sacrificed and autopsied. Organ weights reflecting changes due to the diets and caffeine doses employed are shown in the following table:

TABLE 2

ORGAN WEIGHTS OF RATS FED LABORATORY CHOW AD LIBITUM AND IN RESTRICTED AMOUNTS, WITH AND WITHOUT DAILY CAFFEINE

Organ	Caffeine + chow ad libitum compared with water plus chow ad libitum[a] (%)	Caffeine + 8 g chow daily compared with water plus 8 g chow daily[a] (%)	Caffeine + 8 g chow daily compared with water plus 6 g chow daily[a] (%)
Adrenal glands	+44.4[c]	+40.4[c]	+29.5[c]
Brain	− 0.7	+13.8[c]	+ 3.8
Gastrointestinal tract			
Cardiac stomach	+12.3[c]	+35.3[c]	+24.3[c]
Pyloric stomach	+12.0[b]	+ 0.8	+ 1.5
Small bowel	+18.6[c]	+18.2[c]	+18.7[c]
Cecum	+ 8.0	−16.0[b]	+ 5.1
Colon	+10.2	+24.0[c]	+16.3[c]
Heart	+12.0[c]	+ 4.0	+ 1.0
Kidneys	+ 7.0[b]	+18.0[c]	+12.0[c]
Liver	+18.8[c]	+19.0[c]	+22.4[c]
Lungs	− 9.9	+ 7.4	+ 7.0
Muscle (ventral abdominal wall)	− 2.3	−14.2[c]	− 7.4
Ovaries	+ 8.4	+51.1[c]	+95.6[c]
Skin	− 8.4[c]	− 3.1	− 1.3
Spleen	+14.8	+22.1[b]	+22.4[b]
Submaxillary salivary glands	+76.3[c]	+37.4[c]	+61.5[c]
Thymus	−63.3[c]	−40.1[c]	− 4.9
Residual carcass	− 2.5	− 2.6	− 6.5[c]
Body weight	− 1.4	−14.2[c]	− 3.2

[a] Changes in organ weight are expressed as mean percentage change from control animals given distilled water. Organ weights were calculated as per cent of body weight at autopsy.

[b] Significantly different from control, $P = 0.05$-0.02.

[c] Significantly different from control, $P = 0.01$ or less.

Reducing food intake (groups 6 and 8 of Table 1) increased the toxicity of caffeine. Deaths were of two types: the first, characteristic of those occurring during the first week, was of an "hemorrhagic" nature involving automutilation and hemorrhage; the second, characteristic of later deaths, and resembling the starvation deaths of group 7 table 1, followed a period of tonic-clonic convulsions and increasing weakness.

The main influence of starvation and caffeine toxicity on organ weights as seen in Table 2 was in a relative increase in ovary and thymus gland weights. In general, food intake must be reduced to less than half the ad libitum amounts for an appreciable increase in susceptibility of rats to caffeine toxicity. Until partial starvation approaches zero food intake, such starvation appeared a minor factor influencing caffeine toxicity.

A year following Peters' (1966) report, Peters and Boyd (2496) described a similar experiment in which a cachexigenic diet was given rats in anticipation that this debilitating diet would also increase the toxic effects of caffeine as had starvation. The experimental deaths were similar,

differing principally in the cachexigenic diet of a rancid, biotin-deficient diet of raw egg white, which induced severe cachexia in the experimental rats. The caffeine dose was again 185 mg/kg; the treatment was given for 2 months or until all animals in a comparison group had died. Data regarding treatments and mortality rates are shown in the following table:

TABLE 1

GROUPS OF ANIMALS, TREATMENTS, AND MORTALITY RATES[a]

Group No.	Number of animals	Treatment	Mortality rate[b] (%)	Days to 50% mortality
1	54	Caffeine Rancid diet	89	11
2	30	Caffeine Rancid diet Biotin supplements	97	9
3	36	Caffeine Laboratory chow	8	—
4	18	Caffeine Laboratory chow caloric pair-fed to group 1	5	—
5	46	Distilled water Rancid diet	4	—
6	24	Distilled water Rancid diet Biotin supplements	0	—
7	15	Distilled water Laboratory chow	0	—

[a] Caffeine was administered daily, 6 days a week, in a dose of 185 mg/kg dissolved in distilled water, 20 ml/kg, to groups 1–4; groups 5–7 received 20 ml of distilled water per kilogram daily for 6 days a week.

[b] The mortality rates in groups 1 and 2 were significantly ($P < 0.001$) higher than those of groups 3–7. The percent deaths in group 2 was insignificantly different from that in group 1.

The same clinical measurements noted in Peters' starvation study were made and organ weights and changes are shown in the following table:

TABLE 2

REPRESENTATIVE ORGAN WEIGHTS AND WATER CONTENTS OF RATS FED LABORATORY CHOW OR RANCID DIET AND GIVEN DAILY CAFFEINE[a]

Organ	Weight		Water content	
	Laboratory chow (group 3)	Rancid diet (group 1)	Laboratory chow (group 3)	Rancid diet (group 1)
Adrenal glands	+22.4[c]	+60.0[c]	+0.8	+3.7[c]
Brain	+ 4.4	+30.0[c]	−0.1	0.0
Gastrointestinal tract				
Cardiac stomach	+10.2[b]	+45.5[c]	−0.1	−0.7
Pyloric stomach	+ 6.9	+38.0[c]	+0.3	+2.3[c]
Small bowel	+ 6.7	+45.7[c]	0.0	+5.5[c]
Cecum	+16.1[c]	+36.5[b]	+0.1	+1.7[b]
Colon	+ 5.9	+ 1.5	0.0	+1.4[b]
Heart	+ 1.9	+ 5.1[b]	−0.1	+0.7[b]
Kidneys	− 2.5	+33.5[c]	−0.1	+0.5
Liver	+ 3.4	+48.6[c]	+0.2	−0.4
Lungs	− 3.8	+19.9	−0.1	−0.8
Muscle (abdominal wall)	− 7.3	−38.3[c]	+0.3	+2.2[c]
Ovaries	− 4.1	−21.2[c]	−1.6	−0.1
Skin	− 6.5[c]	−14.1[c]	+1.3	−2.4
Spleen	−17.4	−30.6[b]	−0.4	−0.6
Submaxillary salivary glands	+31.8[b]	+56.1[c]	−0.6	+1.3
Thymus gland	−44.6[c]	−80.3[c]	−0.4	−7.6[b]
Residual carcass	0.0	−10.4[c]	−1.0	+2.5
Body weight	− 3.4	−27.0[c]		

[a] The results are expressed as mean percentage change from control animals given distilled water and laboratory chow ad libitum. Organ weights were calculated as percent of body weight at autopsy and organ water content as percent wet weight.

[b] Significantly different from controls at $P = 0.05$–0.02.

[c] Significantly different from controls at $P = 0.01$ or less.

The results of the cachexigenic experiments were, according to Peters and Boyd, "paradoxical"; the cachexigenic diet increased the sensitivity of rats to caffeine toxicity, but the same dose of caffeine given to rats fed the fresh diet produced earlier death. Apparently, the rats fed the rancid diet ate less food during the first week; thus, the anticipated increased sensitivity to the toxic effects of drugs in malnourished animals need not necessarily be correct, according to Peters and Boyd. The observed changes in clinical measurements and organ weights, etc., were found to be due to a combination of the effects of diet, caffeine and starvation.

Following the determination of the acute oral toxicity of caffeine in the rat, Boyd et al. (394) performed studies of the chronic oral toxicity of caffeine. CBL Wistar rats, 150-200 g body weight were fed Purina chow and water freely. A decreasing series of fractions of the LD_{50}, acute oral, previously determined, was given intragastrically 5 days a week; after

a week or more, the dose was multiplied by 5/7 to establish the average daily dose per week. Each daily dose was given until 60% of the animals had died, or for 100 days whichever occurred first. The doses each day were decreased from a maximum of 264 mg/kg thru 238, 181, 165, 158 and 142 to a minimum of 136 mg/kg; each dose was given to 20 rats. Controls, 8-12 for each dose-level, received only water. Three LD's were established from the data; each parenthetically defined for 0.1 the normal life span, or 100/1000 days: the minimal LD_{100} (0.1L) in which 100% of the animals died from the daily dose within 100 days was calculated to be 191 plus or minus 5.7 mg/kg; the LD_{50} (0.1L) was 150 plus or minus 3.1 mg/kg; and the LD_0 (0.1L) was 110 plus or minus 2.5 mg/kg.

Growth was inhibited only at dose levels above the LD_{50} (0.1L); food intake was unaffected except during the week preceding death, at which time it decreased. Polydypsia was uniformly observed at all except the lowest daily dose, and increased with dose except during the week preceding death when it declined. Diuresis was common at all dose levels above the LD_0 (0.1L). Some animals during the first week of treatment showed blepharitis at high dose levels; after about 1 month of treatment a few animals displayed automutilation, and during the third month, some rats developed alopecia and a dermatitis.

At the higher dose levels, death which occurred within a week of beginning treatment was characterized by convulsions and respiratory failure. Deaths occurring after the first week were preceded by anorexia, a relative oligodipsia and oliguria, loss of body weight, a fall in colonic temperature, proteinuria, aciduria and frequently glycosuria. Gross abnormalities at autopsy were numerous, correlated significantly with the daily dose only in adrenals, pyloric stomach and liver.

Histopathologic observations are summarized in the following table:

TABLE III

The histopathological effects of caffeine on rats

Organ	Daily dose of caffeine (mg/kg)		
	136 and 142	158 and 165	181 and 238
Adrenal glands	Cortical hypertrophy	Cortical hypertrophy	Sinusoids congested
Brain	Mild hyperemia	Mild hyperemia	Meningeal congestion
Gastrointestinal tract			
(a) Cardiac stomach	Mucosal hypertrophy	Normal	Normal
(b) Pyloric stomach	Mucosal hypertrophy Occasional small ulcer	Capillary congestion Occasional small ulcer	Mild inflammation
(c) Small bowel	Mucosal hypertrophy	Mild hyperemia	Moderate inflammation
(d) Cecum	Mucosal hypertrophy	Mild hyperemia	Moderate inflammation
(e) Colon	Mucosal hypertrophy	Normal	Mild inflammation
Heart	Mild hyperemia	Mild capillary congestion	Marked capillary congestion
Kidneys	Mild edema and congestion	Edema and congestion, occasional venous thrombosis and thrombophlebitis	Marked edema and congestio
Liver	Normal	Mild sinusoidal congestion	Cloudy swelling and congesti
Lungs	Bronchopneumonia	Congestion, edema, thrombosis	Congestion, edema, hemorrh
Muscle (abd. wall)	Normal	Weak cross striation	Weak cross striation
Ovaries	Deficiency primary follicles	Mild congestion	Mild congestion
Salivary gland (submax.)	Normal	Normal	Mild hyperemia
Skin	Normal	Occasional dermatitis	Normal
Spleen	Mild loss red pulp	Moderate loss red pulp	Marked loss red pulp
Thymus gland	Moderate atrophy	Marked atrophy	Marked atrophy
Thyroid gland	Colloid deficiency	Mild congestion	

In a 28-day feeding study using young rats weighing about 100 gm, Scott and Chen (2900) compared the effects of feeding caffeine and 1-ethyl theobromine. The test substances were fed to the rats, in groups of 5 animals each, in their standard diet in the concentrations shown in the table below. Records of weight gain revealed little or no depression of growth with concentrations of either compound up to and including 0.1%, while larger amounts inhibited growth somewhat. At the end of the feeding period all of the rats receiving 0.5% of either substance were sacrificed and subjected to post-mortem examination. No gross or microscopic damage was found in the animals which were given 1-ethyl theobromine, with one exception. The animal which died after 15 days on the diet showed pathological changes associated with emaciation. Of the 5 rats on caffeine, 3 were normal, 1 revealed slight pulmonary edema and congestion, and in the other animal hydronephrosis of the right kidney was noted, but no stones were seen.

TABLE 8

The effect on growth of feeding 1-ethyl theobromine and caffeine to young rats for 28 days

DRUG	CONCENTRATION OF DRUG IN FOOD	TOTAL WEIGHT GAIN OF 5 RATS
	per cent	*gm.*
1-Ethyl Theobromine	0.020	477
	0.035	343
	0.070	408
	0.100	348
	0.300	216
	0.500	136*
Caffeine	0.020	511
	0.035	406
	0.070	296
	0.100	436
	0.300	282
	0.500	54

* One rat died on the fifteenth day of the test.

The significance of sex and age as related to caffeine toxicity was the subject of experiments performed with rats by Peters and Boyd (2495) in 1967. Albino Wistar rats of both sexes in 14 groups of varying numbers were given oral daily doses of 185 mg caffeine/kg body weight in 20 ml/kg distilled water; controls were given only 20 ml/kg distilled water orally. The dose of caffeine was of such toxicity that the experiments were ended at 14 days; those not already dead were sacrificed and autopsied. The following table presents the essential data:

TABLE I

Groups, age, body weight, sex, treatment, and mortality rates in rats given caffeine* or distilled water†

Group No.	Age (months)	Initial body weight, mean ± S.D. (g)	Sex	Treatment	Mortality rates at 14 days	
					Incidence	Percent
1	1.5	105±12	F	Water	0/10	0
2	1.5	105±14	F	Caffeine	0/10	0
3	2.5	150±10	F	Water	0/7	0
4	2.5	143±11	F	Caffeine	6/18	33
5	4.5	185±10	F	Water	0/10	0
6	4.5	183±13	F	Caffeine	1/17	6
7	12	275±27	F	Water	0/10	0
8	12	264±28	F	Caffeine	9/13	69
9	1.5	121±10	M	Water	0/10	0
10	1.5	112±12	M	Caffeine	2/10	11
11	4.5	353±18	M	Water	0/9	0
12	4.5	346±33	M	Caffeine	2/13	15
13	12	431±34	M	Water	0/8	0
14	12	447±65	M	Caffeine	10/13	77

*Dose of caffeine was 185 mg/kg per day administered orally in 20 ml/kg of distilled water.
†Dose of distilled water was 20 ml/kg per day administered orally.

The death rate was higher in older animals than in younger, death occurring mainly during the first 2-3 days after beginning treatment. There was little or no difference in the mortality rates of males versus females. The manner in which death occurred distinguished younger from older rats; the young animals died most commonly by automutilation and hemorrhage, whereas the older animals displayed hypokinetic-convulsive deaths. Sex-related responses to the toxicity of caffeine among survivors were evident. Anorexia and loss of body weight were more frequent among male than among female survivors. Loss of muscle weight, but relative weight gains of adrenals and gastrointestinal tract (adrenal hypertrophy is regarded as an index of stress), were greater among males; diuresis was, however, less evident among males. In general, the toxicity of caffeine appeared greater in older, males-than in younger, females.

Cat

Thirty years ago (1944), a possible relationship of caffeine-containing beverages and the pathogenesis of human peptic ulcers was implied in some investigations but not specifically well-studied. Roth and Ivy (2716) employed a method involving a mixture of caffeine, beeswax and mineral oil injected intramuscularly in cats; prolonged and continuous caffeine action results from this technique, similar to that of the modern timed-release encapsulated drugs. Twenty-two experimental cats of various weights were injected alternately into shoulder, thigh, calf and back muscles usually daily with the mixture containing 300 mg caffeine; 10 control animals were similarly treated with the beeswax-mineral oil base only, which had been previously shown to have no gastroduodenal mucosal effect. The experimental animals were sacrificed after showing marked anorexia for 3-5 days, weight loss, tarry stools, convulsions or evidence of complicating pneumonic in-

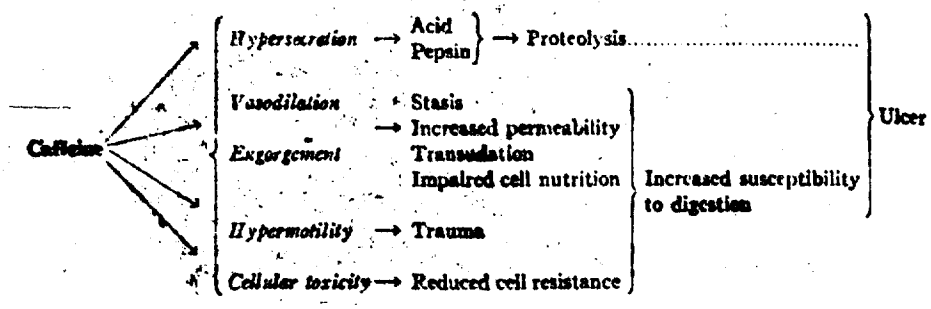
volvement. Diet consisted of milk alternated daily with ground beef heart; water was available freely. Data for the experimental animals are summarized in the following table:

TABLE I

Production of ulcer in cats with caffeine-beeswax mixture

CAT NO.	SIZE	DOSE OF CAFFEINE	NO. OF INJECTIONS	NO. OF DAYS	RESULTS	REMARKS
	lbs.	*mgs.*				
1	4	300	6	6	Prepyloric bleeding ulcer	Sacrificed—convulsions
2	5	300	10	12	Two hemorrhagic areas in antrum	Expired—bronchopneumonia
3	4.8	300	27	33	No hemorrhage, erosion or ulcer	Sacrificed
4	5.3	300	6	7	Two bleeding ulcers in antrum	Expired
5	4	300	6	7	One bleeding ulcer in antrum	Sacrificed—convulsions
6	3.5	300	10	11	Two bleeding ulcers in antrum	Sacrificed
15	4.8	300	8	10	One bleeding prepyloric ulcer	Expired—antral erosion, duodenal hemorrhage
17	5.5	300	17	23	No hemorrhage, erosion or ulcer	Sacrificed
18	5.5	300	6	7	Antral erosion, duodenal hemorrhage	Expired—bronchopneumonia
19	5	300	16	22	No hemorrhage, erosion or ulcer	Sacrificed
21	4.5	300	2	3	Multiple bleeding erosions and ulcers	Expired
22	4.5	300	5	5	Shallow bleeding prepyloric ulcer	Expired—convulsions
25	4.3	300	30	38	One ulcer, two erosions in antrum	Expired—pregnant at start of experiment
30	6.8	300	11	16	No hemorrhage, erosion or ulcer	Expired—bronchopneumonia
31	5.5	300	3	4	Prepyloric ulcer	Expired
33	4.8	300	11	15	Prepyloric submucosal hemorrhage	Expired
35	5.5	300	30	38	No hemorrhage, erosion or ulcer	Expired
36	5.0	300	30	39	No hemorrhage, erosion or ulcer	Sacrificed
37	5.3	300	11	15	No hemorrhage, erosion or ulcer	Expired—bronchopneumonia
38	7.8	300	11	16	No hemorrhage, erosion or ulcer	Expired—convulsions
39	5	300	30	37	No hemorrhage, erosion or ulcer	Sacrificed
40	3.5	300	8	11	Bleeding prepyloric ulcer, three erosions	Expired
Ave.	5.0	2.5 gms.	8.4	10.2	11 of 22 cats developed erosions or ulcers	

The average weight of the 22 experimental cats was 5 lbs, or about 2.3 kg; the average total dose was 2.5 g or about 1 g/kg body weight given over a period of an average of 10 days. Half, or 11 of the 22 animals, developed bleeding erosions or ulcers in the mucosa of stomach antrum and prepyloric regions. In 5 of the animals, multiple lesions were observed. These mucosal defects or ulcers grossly resembled those occurring spontaneously in man. A number of macro- and microphotographs of the gastric mucosa in experimental animals accompany the report. From the results of studies by other investigators as well as from their own, the authors postulated the following diagrammatic representation of the possible roles of caffeine in the pathogenesis of gastric ulcers:



In summary, Roth and Ivy suggest "that the use of caffeine beverages be restricted in the management of the peptic ulcer patient".

Man

Reimann (2623) reported in 1967 a case of caffeinism due to the excessive intake of coffee by a 39 year old woman (whom the author stated was psychoneurotic). Symptoms of caffeinism included low-grade fever, insomnia, anorexia, and irritability. The woman had been drinking 15 to 18 cups of coffee daily for an unspecified period of time. When coffee was restricted to 1 cup per day, the symptoms disappeared and no withdrawal problems were encountered.

III. Long-Term Studies

None Found

IV. Special Studies

Pharmacology

Goodman and Gilman (1155) summarized in 1970 the physiological effects of caffeine in humans. The first is CNS stimulation, involving the cortex, medulla, and spinal cord. This effect is useful in treating poisoning by CNS depressants, such as morphine. Children tend to be more sensitive to

caffeine than adults. The cortical stimulating effects of drinking 1 or 2 cups of coffee (150 to 250 mg caffeine) are increased motor activity, decreased reaction time, and decreased drowsiness and fatigue. Too much caffeine can lend to hyperesthesia and depression. Stimulation of the medulla causes increased respiratory minute volume, at doses higher than that required for cortical stimulation. A second major type of effect of caffeine involves the cardiovascular system. Depending on dosage and other factors, caffeine can cause an increase in coronary blood flow, tachycardia, systemic blood vessel dilation, and cerebral vasoconstriction (which may explain the use of caffeine in headache remedies). A third effect of caffeine is the relaxation of smooth muscle - especially bronchial muscle, which makes caffeine useful in treating bronchial asthma. Two other muscular effects are the stimulation of cardiac muscle and strengthening of voluntary muscle contraction. The latter effect increases the capacity for muscular work in humans. Caffeine is a mild diuretic and stimulates gastric secretion, which can cause gastric irritation and ulcers. There are a number of metabolic effects - slight increase in basal metabolism rate, promotion of creatinuria in humans, inhibition of urea formation from ammonium salts, changes in the calcium dynamics of muscles in vitro, and inhibition of cyclic nucleotide phosphodiesterase (the enzyme which catalyzes the conversion of cyclic 3',5'-AMP to 5'-AMP).

Cardiovascular Disease

Klatsky et al. (1700) reported in 1973 a study controlled for cigarette smoking and 5 other risk factors in which no significant correlation between coffee-drinking and a first myocardial infarction was found. Each of the 464 subjects in the study had a myocardial infarction, after having undergone an MHC, (multiphasic health checkup), between 1964 and 1970 in which the question "Have you usually in the past year, drunk more than six cups of coffee per day?". These subjects were compared to controls with no myocardial infarctions, divided into two types - ordinary and risk. The only group in which there was a significant correlation was in women between 55 and 64 years of age, where more risk controls drank over 6 cups of coffee per day than ordinary controls. No correlation between patients with a myocardial infarction and risk controls could be made in the study. The overall result was that 20% of all patients with myocardial infarction, of all ordinary controls, and of all risk controls drank over 6 cups of coffee per day. The authors stated that since coffee-drinking and cigarette smoking are highly correlated habits, the data implicating coffee as a risk factor in heart attacks may be due to cigarette smoking. The relationship of myocardial infarction and coffee drinking is shown in the following table:

Table 2.—Percentages of Myocardial Infarction Patients and Controls Who Reported Drinking More Than Six Cups of Coffee Daily

Age, yr	% Drinking >6 Cups Daily: MI Patients	Ordinary Controls	Risk Controls	No. of Pairs* MI Patients vs Risk Controls
Total	21.4	18.9	22.3	457
>65	9.4	13.6	10.7	148
55-64	23.7	17.7	25.3	152
<55	30.4	25.0	30.2	157
Men	22.6	20.6	22.9	328
>65	8.2	12.2	11.1	98
55-64	25.0	20.2	22.7	108
<55	21.1	27.6	32.6	122
Women	18.3	14.6	20.8	129
>65	11.8	16.3	10.0	50
55-64	20.5	11.4†	31.8†	44
<55	25.0	16.2	22.2	35
Prior clinical diagnosis of coronary heart disease other than MI				
Yes	18.1	11.7	19.2	94
No	22.2	20.8	23.1	363

*In each subgroup and total group, the number of pairs of myocardial infarction (MI) patients vs ordinary controls and of ordinary controls vs risk controls was within two of the number of pairs of MI patients vs risk controls.
†$P<.05$.

Little et al. (1964) reported in 1966 that the drinking of coffee has been positively correlated with elevated serum-lipids in over 100 male patients with coronary heart disease, aged 40 and over. The patients had recovered from a myocardial infarction at least 3 months before the study. Healthy subjects were used as controls - no correlation between coffee and serum lipids was found in the group. The normal, dietary intake of coffee and other foods was recorded for 7 days for the study. Correlations with tea were negative; therefore, the authors did not believe that the increase in serum lipids was due to caffeine.

Walker and Gregoratos (3430) in 1967 found no significant correlation between coffee consumption and myocardial infarction in a study of 100 male military personnel who had survived a myocardial infarction, and 72 controls. All subjects were 40 years old or less.

Paul (2468) states in his article of 1968 that there is a considerable amount of conflicting evidence about the role of caffeine in heart disease. The author observed a relationship between angina pectoris and myocardial infarction to men who drank 5 or more cups of coffee per day. The observation was over a period of 8 years in a group of 1700 men from 40 to 55 years old employed at an electric company in Chicago. The unexplained

observation was that among those who died, the death rate was highest when the men either did not consume coffee or drank 5 or more cups daily. The following table shows coffee intake and coronary disease:

Table 1. Coffee Intake and Coronary Disease*

Cups of Coffee Consumed per Month	Subjects	Angina		Myocardial Infarction†		Deaths From Coronary Disease	
		Cases	Prevalence Rate	Cases	Prevalence Rate	Number	Prevalence Rate
None	136	7	0.05	4	0.03	8	0.06
1-49	239	9	0.04	7	0.03	3	0.01
50-99	553	16	0.03	13	0.02	4	0.01
100-149	463	25	0.05	12	0.03	3	0.01
150 or more	327	23	0.07	17	0.05	6	0.02
	1,718	80		53		24	

*Data obtained in an eight year study of a population group of men 40 to 55 years of age employed by Western Electric Company.

†With survival.

Saytanov (2827) in 1971 reported the caffeine poisoning of a 40 year old man from occupational exposure (inhalation) to powdered caffeine sodium benzoate during cleaning a room by shoveling a large amount of this material. The amount inhaled was unknown; however, the room contained about 500 kg of powdered caffeine sodium benzoate. Toxic symptoms included chest pains, heart palpitations, chills, muscular cramps, hyperemia in the skin of the face and chest, euphoria, respiratory difficulties, motor disturbances increased arterial pressure, and alterations in the EKG - subepicardial ischemia of the myocardium and sinus tachycardia. The poisoning was not fatal and the man was normal in 2 weeks. The myocardial disturbances were thought to be due to the release of catecholamines due to the stress of the caffeine overload. The catecholamines would be supplied in excess to the heart muscle, resulting in necrosis and hypoxia.

Jick et al. (1562) reported a study in 1972 in the Boston Collaborative Drug Surveillance Program, in which patients who had acute myocardial infarctions drank significantly more coffee than patients who had not had myocardial infarctions. This finding was based on the coffee- and tea-drinking habits of 276 patients who had myocardial infarctions and 1104 matched controls who had other types of diseases. The correlation between coffee-drinking and myocardial infarction could not be explained in terms of cigarette-smoking. The study showed that those who drank over 5 cups of coffee per day had a risk twice as high as those who abstained from coffee. Since the drinking of tea, which contains as much caffeine as coffee - 100 to 150 mg per cup, could not be correlated with myocardial

infarction in this study, Jick et al. did not believe that caffeine could be responsible for the data because both tea and coffee contain 100-150 mg caffeine per cup. The following tables summarize the data:

TABLE I—COFFEE AND TEA CONSUMPTION AMONG PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND MATCHED CONTROL PATIENTS

Group	Consumption (cups/day)			
	0	1–5	6+	Total
Coffee:				
M.I.	48	188	40	276
Controls	256	748	100	1104
Risk ratio	*1·00*	*1·34*	*2·13*	
Tea:				
M.I.	119	146	11	276
Controls	433	610	61	1104
Risk ratio	*1·00*	*0·87*	*0·66*	

M.I. = Myocardial infarction.

TABLE II—COFFEE CONSUMED AMONG PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND MATCHED CONTROL PATIENTS BY SEX, AGE, AND HOSPITAL

—	Coffee consumption (cups/day)			
	0	1–5	6+	Total
Males:				
M.I.	30	132	31	193
Controls	174	508	90	772
Risk ratio	*1·00*	*1·51*	*2·00*	..
Females:				
M.I.	18	56	9	83
Controls	82	240	10	332
Risk ratio	*1·00*	*1·06*	*4·10*	..
Age < 59 yr.:				
M.I.	18	75	26	119
Controls	108	295	73	476
Risk ratio	*1·00*	*1·53*	*2·14*	..
Age 60+ yr.:				
M.I.	30	113	14	157
Controls	148	453	27	628
Risk ratio	*1·00*	*1·23*	*2·56*	..
U.S. hospitals:				
M.I.	18	91	27	136
Controls	97	391	56	544
Risk ratio	*1·00*	*1·25*	*2·60*	..
Non-U.S. hospitals:				
M.I.	30	97	13	140
Controls	159	357	44	560
Risk ratio	*1·00*	*1·44*	*1·57*	..

TABLE III—PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND CONTROL PATIENTS IN RELATION TO CURRENT SMOKING STATUS AND COFFEE CONSUMPTION

Group	Coffee consumption (cups/day)			
	0	1–5	6+	Total
Non-smoker:				
M.I.	16	55	5	76
Controls	104	250	8	362
Risk ratio	*1·00*	*1·43*	*4·06*	
Up to 1 pack cigarettes per day:				
M.I.	9	52	12	73
Controls	53	185	29	267
Risk ratio	*1·10*	*1·83*	*2·69*	
More than 1 pack cigarettes per day:				
M.I.	8	24	14	46
Controls	28	75	29	132
Risk ratio	*1·86*	*2·08*	*3·14*	
Ex-smokers:				
M.I.	12	38	6	56
Controls	48	153	16	217
Risk ratio	*1·63*	*1·61*	*2·44*	
Smokers of variable numbers of cigarettes, pipes, cigars:				
M.I.	3	19	3	25
Controls	23	85	18	126
Risk ratio	*0·85*	*2·45*	*3·08*	

Mutagenicity

The dominant-lethal method was used by Thayer and Kensler (3220) in 1973 to test the possible mutagenicity of caffeine in mice. Three experiments were conducted using CD-1 mice: male mice received caffeine in the drinking water for 8 weeks at levels of 3.6, 13.4, 49 and 122 mg/kg after which matings to untreated females were performed for an additional 8 weeks; a second experiment tested male mice for enhancement of radiation induced dominant lethal mutations by acute doses of caffeine administered intraperitoneally before and after an irradiation dose of 100 r from a Co^{60} source; the third experiment tested male mice given caffeine in the drinking water for 16 weeks after which they were either irradiated with a dose of 100 r, or were injected intraperitoneally with a single dose of the chemical mutagen triethylene melamine (TEM), at 0.2 mg/kg. Matings of the treated males with untreated females in the second and third experiments proceeded in the same manner as in the first experiment.

The only significant effect noted in the first experiment was an apparent reduced fertility in the males at the high caffeine levels (49 and 122 mg/kg/day). Early deaths per pregnant female, and the mutation index data showed no significant effects produced by any level of caffeine.

Comparisons of caffeine with caffeine plus Co^{60} gamma rays, or gamma rays alone, produced no appreciable effects of the caffeine on pregnancies, implants or embryonic deaths in the second experiment.

Fertility, litter size or the induction of dominant-lethal mutations by gamma rays or TEM were not affected or modified by caffeine pretreatment in the third experiment.

Caffeine was tested by Cattanach (517) in 1962 for its ability to induce translocations in mouse chromosomes, particularly of the type which reduces the fertility in males, and is cytologically detectable. Inbred male mice were given 0.3% solutions of caffeine as drinking water for a period of 3 months to insure that the spermatagonia had been thoroughly exposed to caffeine. The treated males were mated to virgin females and the offspring examined at 3 weeks of age for morphological abnormalities; only the sons were kept and mated in turn to untreated virgin females at 5 weeks of age. Litter sizes from these F_1 sons were recorded; of 201 males, only 13 produced litters of fewer than 8 offspring. Cytological studies of the 13 animals showed 11 to be quite normal and 2 abnormal, but none with a translocation of the type looked for.

Contrary to the essentially negative results of the translocation tests, a reduction in fertility of the caffeine-treated animals was detected; litter sizes were smaller than in controls. This difference increased with time after the caffeine treatment was stopped.

Some possible explanations for caffeine-induced reduction in fertility were advanced by the author.

Silzynski (3007) in 1971 found that caffein produced chromosomal

alterations - stickiness, clumping, extrusion of chromatin from the nuclei, fragmentation, and gap formation - in spermatogonia of mouse testes cultured in vitro in a saturated caffein solution. The caffein solution contained 0.9% NaCl. Each testis was kept in 1 ml of the solution for 25 minutes, 1, 2, 4, 6, 16, 24, or 36 hours, with controls in saline only. Except for some necrotic phenomena, no changes occurred in the control testes. In the test cultures, there were also unusual changes in the spermheads of developing spermatozoa - gaps appear in the cell and they lost their stainable substance. The author stated that caffeine affects the F+ material in cell nuclei, but not the chromosome movement.

Epstein et al. (884) in 1970 studied the mutagenicity of caffein in the Swiss mouse, strain ICR/Ha, using the dominant lethal test. Male mice, 8-10 weeks old, were injected i.p. once with caffein in tricaprylin or distilled water at an injection volume of 0.1 ml. The dosage ranged from 168 to 240 mg/kg. Control groups received one of the vehicles alone. The 175 mg/kg dose was given twice, 24 hours apart. After the caffein was given, the males were each allowed to mate with 3 virgin females for weekly intervals for 3 to 8 weeks. The females were autopsied 13 days after the exposure to the males, and the number of liver and dead uterine implants and early and late fetal deaths were determined. Caffeine did not increase early fetal deaths or preimplantation losses. The number of pregnancies was significantly reduced when females were mated with caffeine treated males.

Epstein and Shafner (883) in 1968 discussed the method of screening caffeine for mutagenicity, using the dominant lethal test in mice. This test consists of mating caffeine-treated males with several new, untreated virgin females weekly for 8 consecutive weeks, which covers the spermatogenic cycle in the mouse. The females are then autopsied 13 days after the mid-week of their exposure to the males. The mutagenic activity is measured by the number of fetuses which die in vitro due to mutations in the sperm cells. The mutagenic index is then calculated using this formula:

$$\frac{\text{deciduomata (early deaths) + late deaths}}{\text{total implantations}} \times 100$$

Epstein and Shafner administered 168 mg/kg, i.p., in 0.1 ml volume of tricaprylin solution. to 10 male Swiss mice. Ten controls were given the tricaprylin alone. Two hours after the injection, the males were mated with females, as explained above. No significant mutational activity due to caffeine was found. The mutational index was 0 with caffeine-treated animals, and 1 with control animals.

Kuhlmann et al. (1829) in 1968 reviewed some of the findings on the mutagenic effects of caffeine on human and mouse cells. Both cell growth and RNA synthesis of HeLa cells were inhibited by concentrations of caffeine

above 0.2 mg/ml (Ostertag et al.). Ostertag et al. also found changes in HeLa cell morphology - they became more spherical and lose their attachment to the Petri dish glass - at caffeine concentrations greater than 0.1 mg/kg. At a 1% concentration (10 mg/kg), caffeine causes the nuclear material to be extruded from the cells, which the authors feel is a unique effect. Caffeine has also been found to induce chromosome breaks, which do not rejoin, in both HeLa cells and leucocytes, at doses below 0.5 mg/kg after 1 hour exposures. Chart 4 indicates that the number of breaks is proportional to the dose of caffeine up to a certain point, after which the breaks are more than linear.

In mice, Lyon et al. found no significant increase in the mutation rate when either males or females were treated with caffeine. Cattanach found decreased fertility produced by treating male mice with caffeine, which Kuhlman et al. suggest was influenced by the increase in the number of dominant lethal mutations produced after treating the males with 0.025 to 0.5% caffeine in the drinking water (see Chart 10).

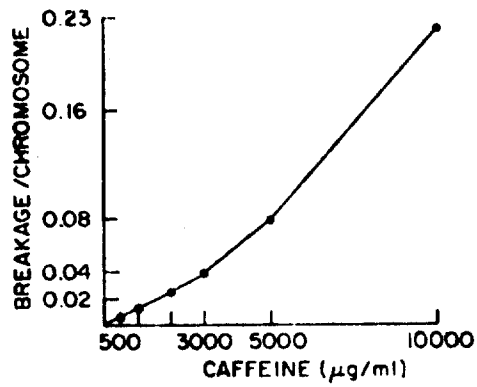


Chart 4. Breakage induced by caffeine in HeLa cells. Dose dependence [Ostertag *et al.* (26)].

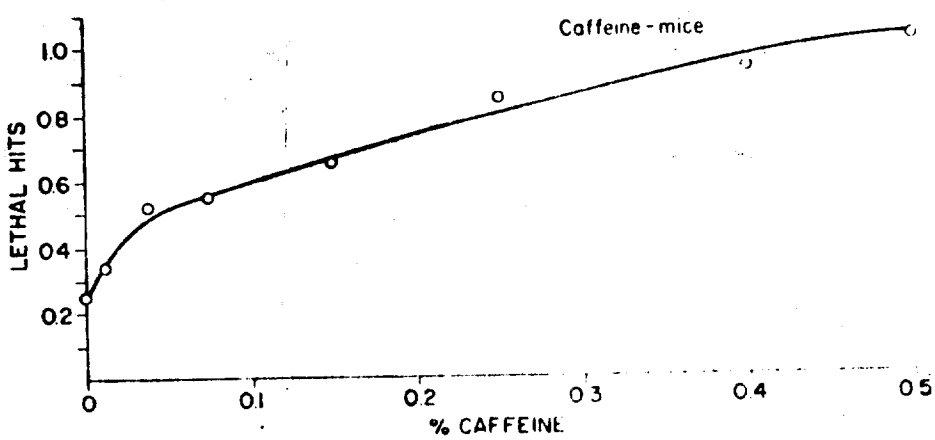


Chart 10. Dominant lethals induced by caffeine in mice. Correction applied. Poisson distribution.

The authors also stated that since caffeine only affects cells during DNA replication, only male germ cells would be significantly affected, because female germ cells stop replicating after birth of the female.

In Adler's (21) review of literature in 1970 on caffeine mutagenicity, research on Russian rabbits by Stieve was reported, in which daily s.c. doses of 50 to 200 mg/kg caffeine were given. The doses were gradually increased from 50 mg/kg to 200 mg/kg in daily increments of 25 mg/kg to habituate the rabbits to the higher level, since 200 mg/kg at once was usually lethal. The treated males were mated with untreated females. Up to 70% of the litters did not survive for one week after birth. Adler did not believe that Stieve's experiment was adequately controlled.

The work of Lyon et al. was reported by Adler, in which male, 101/H mice and female C3H/HeH mice were given 0.1% caffeine in drinking water for 7 weeks. The offspring of these mice (F_1) were treated for 10 weeks, in which they received a total of 300 mg caffeine. The F_1 animals were mated with PCT mice which had homozygous recessive genes in 7 loci. The F_2 generation showed no evidence of dominant or recessive mutations. Lyon et al. also mated treated males with females in a 1:5 ratio for 4 weeks. The pregnant females were autopsied, and no evidence of lethal mutations, as shown by dead implants and corpora lutea graviditatis, were found.

Adler reported the work of Cattanach, in which inbred JU males were given 0.3% caffeine in drinking water for 3 months. When the males were sequentially mated with groups of untreated virgin females in a 1:3 ratio weekly over 6 weeks, the size of the litters was smaller than that of control matings during the first 3 weeks. The F_1 males of litters smaller than 8 were mated at 6 weeks of age with Q-females in a 1:2 ratio. Of these 201 males, only 13 of them sired litters smaller than 8. Only 2 of these 13 males had an abnormal cytology in their testes, but no evidence of translocations. Lethal mutations were ruled out as a factor in the decreased litter sizes.

Adler (21) studied the mutagenicity of caffeine in two similar studies one year apart, on the effects of caffeine on spermatogenesis in male mice. The mice were all inbred strain C3H and were 10 to 11 weeks old. In the first experiment, 15 males were given one dose of 250 mg/kg caffeine in 1 ml 0.9% saline i.p.; 5 controls were given the saline alone; in the second experiment only the number of animals used was changed. The dosage of caffeine was tolerated by the mice. One day after the caffeine administration, each male was mated with 3 virgin females for weekly periods, 7 times. At 14.5 to 16.5 days of pregnancy, the pre- and post-implantational egg losses were determined. The pre-implantational loss was found by the ratio of implants to corpora lutea graviditatis. The post-implantational loss equalled the number of dead embryos. No significant differences in implantational egg losses were found between tests and controls. There was a significant decrease in the frequency of copulation in caffeine-treated males. There was also a slight increase in pseudopregnancies.

Adler and Roehrborn (23) in 1969 investigated the effect of chronic caffeine dosage on meiotic chromosomes in spermatogonia in male mice, C3H inbred, and (101 X C3H) F_1 hybrids. The caffeine was given in the drinking water at concentrations of 0.0023%, 0.01%, and 0.5%. The lowest dose was considered equal to about 2 cups of coffee per day in humans. Higher levels were given because mice may metabolize coffee faster than humans. Treatment periods were from 245 to 351 days, and 1 to 3 mice were in each group. Control mice were given no caffeine in their water. The only mutations were a translocation in a control. An increase in univalent chromosomes in both the lowest and highest dosage groups of test animals was not significantly different from corresponding controls. In the C3H strain at the 0.01% level, there were significantly more univalent chromosomes, but the authors believed this was a chance occurrence.

In a study using lymphocyte cultures from the blood of healthy human subjects, Timson (3237) in 1972 found that caffeine was cytostatic (no cells in mitosis) at 10^{-2} M and antimitotic (rate of mitosis decreased) at 10^{-3} M, but not at 10^{-4}. The antimitotic activity was 41% of the controls at 10^{-3} M and 0 at 10^{-2}M. At 10^{-4} M, there was a significant difference in the response of lymphocytes from males and females - antimitotic activity was 192% of the controls in females, 68% of the controls in males. The author suggested that the lack of visible evidence of the mutagenic activity of caffeine in humans may be because the antimitotic and mutagenic tresholds are equal, so that affected germ cells cannot divide.

Ostertag et al. (2437) in 1965 found that caffeine caused chromosome breakage of HeLa cells in culture and that the amount of breakage was proportional to doses of caffeine up to 10 mg/ml. Above 10 mg/ml, the breakage was greater than linear. Few translocations were found when caffeine was used, contrary to that caused by other mutagens, such as acridine dyes or actinomycin. Apparently, caffeine must be added before or during DNA replication for the breaks to occur. The authors stated that the amount of damage would be in the normal range of mutations.

Roehrborn (2677) reported in 1972 the results of an investigation into the mutagenic effects of chronic exposure to low doses of caffeine in mice. Male mice of the C3H and (101 X C3H)-F1-hybrids were treated with 3 different caffeine concentrations in the drinking water; 3.4 to 3.6 mg/kg/day; 14.9 mg/kg/day; and 17.3 mg/kg/day. Treatment lasted for from 245 days to 351 days. A small number of C57BL mice were also included in the study. At specific times after treatment was begun, treated (and untreated control) males were mated to virgin females of the same strain; on the 15th day of pregnancy, the females were sacrificed and the number of implants, living and dead, were determined. An increase in dead uterine implants was the criterion for induced dominent lethal mutations. A number of different experiments were performed, the details of which may be seen in the report included in the Documents Section of this Monograph. Briefly, all efforts to demonstrate a significant induction of dominant lethal mutations in mice by caffeine were unsuccessful.

Teratogeny

Snigorska and Bartel (3024) in 1970 injected doses of caffeine of 250-800 mg/kg s.c. into pregnant white mice between the 7th to the 14th day of gestation; controls were given saline s.c. The 600-800 mg/kg doses resulted in the death of the mothers within several minutes to several hours. The 500 mg/kg dose resulted in the death of 32% of the mothers. The fetuses examined from pregnant mice which went full term (20 days) had various developmental disorders: in the skeletal system, such as in the digits and some cleft palates; s.c. hematomas, harelip and resorption of fetuses. These defects are similar to those found by Nishimura and Nakai (1960). Doses of 400 mg/kg produced developmental disorders in 73% of the fetuses and resorption of embryos and fetuses in 27% of cases. Doses of 300 mg/kg caused resorption of embryos or fetuses in 30% of cases and 8% developmental anomalies. Caffeine injected in doses of 250 mg/kg body weight caused intrauterine death and resorption of fetuses in 33% of the mice without any developmental disorder in surviving progeny.

Nishimura and Nakai (2360) in 1960 gave 100 pregnant, SMA mice one injection of 1% caffeine in aqueous solution i.p. during the 7th to the 15th day of pregnancy. The maximum tolerated dose - 250 mg/kg - was given. Fetuses from 25 untreated mice served as controls. The placental size, shape, color and embryonic body weights were all within normal range. Caffeine injections between days 7 to 14 of pregnancy produced from 3 to 18% death of the fetuses. From days 9 to 14, in 18 to 43% of the fetuses, various malformations were found. These malformations involved the skeletal system for the most part, predominantly cleft palate and digital defects. The digital defects were often accompanied by hematomas (See tables I and II).

TABLE I. Effects of Intraperitoneal Injection of Caffeine* in Pregnant Mice Observed at Term.

Day of inj.	No. of mice	No. of complete resorptions	Young		
			Total No.	% dead	% abnormal
7	4	2	11	18	0
8	5	0	36	6	0
9	11	2	45	11	2
10	6	0	40	3	38
11	10	0	57	12	19
12	8	1	41	17	41
13	7	0	51	8	43
14	7	1	44	18	18
15	3	0	24	0	0
Uninjected controls	25	0	225	2	0

* 1% aqueous solution, 0.25 mg/g body wt.

TABLE II. Number and Types of Malformations Observed in Offspring of Pregnant Mice Given Intraperitoneal Injections of Caffeine.*

Day of inj.	Abnormal young No.	No. of young with specific malformations in: Digits Fore	Hind	Joints†	Palate	Hematoma	Other
9	1				1		
10	15	3	10	3	2		1
11	11	8	8		1	1	
12	17	14	9	4	10	12	
13	22	14	7	2	9	15	1
14	8	1	8	2		4	

* 1% aqueous solution, 0.25 mg/g body wt.
† This column includes clubfoot as well as joint malformations.

Fujii et al. (1044) in 1969 divided 165 pregnant mice (strain ICR-JCL, 9-13 weeks old) into 4 test and 4 control groups on the 12th day of pregnancy. Group Ia mice were given 200 mg/kg caffeine in a (1% aqueous solution) once in the A.M., s.c.; Group IIa mice were given this dose i.p.; Group IIIa mice were given a 100 mg/kg dose twice at a 2 hour interval in the A.M., i.p.; Group IVa mice were given a 100 mg/kg dose twice at a 4 hour interval (9:30 A.M. and 1:30 P.M.). In the control groups, equal volumes of saline were injected in the same ways as in the test groups. On day 18 of pregnancy, the mice were autopsied and the conditions of the fetuses were examined. No maternal deaths occurred, although the caffeine injections produced slight dyspnea and convulsions in the first 2 test groups and dyspnea and reduced activity in IIIa and IVa. All of the test groups had higher incidences of resorbed fetuses and fetal abnormalities than the control groups (see Table 2). The lethal effect of one s.c. injection of caffeine was more severe than with one i.p. injection. One i.p. injection was more teratogenic than when it was given in 2 half doses, but the 2 doses were more lethal.

TABLE 2. Classification of abnormal fetuses according to type of defects.

Group	No. of live fetuses	No. of fetuses with abnormalities	Incidence of fetuses with each abnormality (% out of live)				
			Cleft palate	Micrognathia	Defect of digits	Hematoma	Clubfoot
Ia	248	51	48* (19.4)	15* (6.0)	1 (0.4)	15* (6.0)	3 (1.2)
IIa	251	46	41*+ (16.3)	11*+ (4.4)	–	11*+ (4.4)	3 (1.2)
IIIa	265	18	16* (6.0)	1 (0.4)	1 (0.4)	5* (1.9)	2 (7.5)
IVa	262	16	5 (1.9)	–	–	–	11* (4.2)
Ib	244	1	–	–	–	–	1 (0.4)
IIb	218	3	–	–	–	–	1 (1.4)
IIIb	238	1	1 (0.4)	–	–	–	–
IVb	250	1	1 (0.4)	–	–	–	–

* Significantly different from those of respective control groups ($P<0.01$)
\+ Significantly different from those of group IIIa and IVa ($P<0.01$)
++ Significantly different from that of group IVa ($P<0.01$)

Fujii and Nishimura (1046) in 1972 divided pregnant Sprague-Dawley rats, 10 weeks old, into 7 groups and treated them as follows:

	No. of Pregnant Rats/Group
Group I: fed the diet containing 0.25% caffeine throughout gestation	11
Group II: fed the diet containing 0.50% caffeine throughout gestation	13
Group III: fed the basal powdered rat diet throughout gestation. This group served as the control for groups I and II. Pregnancy of animals in groups I, II and III was terminated on day 21 of gestation	13
Group IV: fed the diet containing 0.50% caffeine from day 1 to 7 of gestation	16
Group V: fed the same caffeine-containing diet from day 8 to 14 of gestation	15
Group VI: fed the same caffeine-containing diet from day 15 to 21 of gestation	13

	No. of Pregnant Rats/Group
Group VII: fed the basal powdered diet throughout gestation. This group served as the control for the groups IV, V and VI. Pregnancy of the animals in the groups IV, V, VI and VII was terminated on day 22 of gestation	13

Females in Group II gained significantly less weight than either of the controls or group I. The average daily caffeine intake during pregnancy was 180 mg/kg in group I and 330 mg/kg in group II. Embryotoxic effects, such as increased fetal resorption, decreased live fetal weight, generalized edema, s.c. hemorrhage, delayed ossification, and various malformations, were found in both I and II. The maternal capillaries of the group II placentas were congested in most cases. The total cholesterol concentration in the maternal sera was not significantly different than that of the controls. The only dose-dependent parameters observed were fetal resorption and decreased live fetal weight. In groups IV, fetal weight was depressed significantly and there was a high incidence of hydronephrosis. The group V fetuses also showed a weight depression; plus a very high number of esophageal defects, tail malformations (short or kinky tails) and a high incidence of fetal resorption.

Only in group VI was the occurrence of edema in live fetuses found (95.8%). The most severe retardation of ossification occurred, a significant increase in nucleated red blood cells, and fetal weight depression occurred in VI also. The authors stated that the results of groups V and VI show that caffeine causes the severest teratogenic effects when given during days 8 to 14 of gestation; severe edema was produced during days 15 to 21.

Bertrand et al. (269) reported in 1965 the results of teratogenic studies using caffeine given orally to mice and rats. The mouse studies were inconclusive, only one fetus of 38 produced by 8 females of the CNRS strain treated with 50 mg/kg caffeine during the 6th to 18th day of gestation, showed an anomaly of the development of the phalanges. A second test with Swiss mice produced only normal fetuses.

The rat studies with the Wistar strain showed an embryo-fetal resorption proportional to the dosage used. The animals averaged about 200 g in weight, and were given oral doses of caffeine of 75, 100, 125 and 150 mg/kg. The caffeine was given for 8 days before impregnation and was continued throughout gestation; all animals were sacrificed on the 20th day of pregnancy and fetal products examined. A study of 731 fetal products showed anomalies peaking at about 20% at the 125 and 150 mg/kg doses. The fetal anomalies were specific malformations (ectrodactylias) found only in the caffeine-treated animals. A follow-up report by Bertrand et al. (268) in 1970 described experiments with various strains of rats (the genotype appeared to condition sensitivity to caffeine in the female); with mice, no tests produced ectrodactyly; with female rabbits,

ectrodactyly in the form of an absence of a thumb on the front feet was observed in 6 individuals from 3 litters of 14 female rabbits. The female rat appeared to be sensitive to the teratogenous effects of caffeine in terms of genetic predisposition; somations rather than mutations.

Food and Drug Research Laboratories, Inc. (983) in 1973 submitted progress reports to the FDA on teratologic evaluations of caffeine on mice, rats and hamsters; a final report on rabbits was also given. The tentative conclusions of the first three studies were in the following form:

> "The administration of up to (A) mg/kg (body weight) of the test material to pregnant (B) for (C) consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

For mice, A = 36 mg/kg; B = mice; C = 10 consec. days.

For rats, A = 22.5 mg/kg; B = rats; C = 10 consec. days.

For hamsters, A = 30 mg/kg; B = hamsters; C = 5 consec. days.

In the rabbit studies, A = 7 mg/kg; B = rabbits; C = 13 consec. days. At higher dose levels of 32.5 mg/kg, however, there appeared to be an increase in maternal mortality with a decreased fertility rate. No clear indication of teratogenicity even at this level was observed.

Carcinogenesis

Goldstein and Warren (1142) in 1962 reviewed the hospital records of all male patients entering Stanford-Lane Hospital, San Francisco between 1932 and 1958 and San Francisco County Hospital between 1941 and 1957 under the diagnostic heading of "gastric carcinoma" and "Carcinoma of the colon". In order to be included in the study the record had to show confirmation by biopsy, autopsy or exploratory laparotomy, and the record had to contain definite information on the intake of beverages containing caffeine. A total of 136 records in "carcinoma of the stomach" and 66 on "carcinoma of the colon" was included. The two groups of patients did not differ in any important way from each other from the healthy United States population with respect to caffeine consumption. The author concluded that an hypothesis that caffeine plays any significant role in the etiology of gastric carcinomas could probably be rejected.

Cole (617) reported in 1971 finding a positive correlation between bladder cancer and coffee-drinking in a case-control study. A total of 468 cases and 498 controls were asked if they drank coffee and if so, how many

cups per day; the subjects were also asked about their cigarette-smoking habits. For men and women, those who drink less than one cup per day were found to have a lower risk of getting bladder cancer. The correlation between bladder cancer and coffee-drinking was stronger for women (49% risk) than for men (24% risk). The author believes that about 1/3 of the cases in the U.S. could be attributed to coffee-drinking. Caffeine was not specifically identified as the contributing factor in this correlation.

Timson (3236) in 1971 added to the report of Cole on the positive correlation of coffee-drinking and bladder cancer being higher for women than for men. Since about 10^{-4} M caffeine (equivalent to 8 cups coffee or 11 cups of tea) stimulates mitosis in lymphocytes of women and decreases mitosis in those of men, this might explain the sex differences. Therefore, the author thought that caffeine might tend to stimulate bladder cancer cell growth.

Zeitlin (3567) in 1972 did not believe that Cole's case-control study on the incidence of bladder cancer among coffee-drinkers was supported by laboratory studies. The author cited his long-term feeding study (2 years), in which male and female weanling Sprague-Dawley rats were given 5% instant coffee in a lab chow diet, of which 3.6% was caffeine (0.18% of diet). The daily consumption equalled about 85 cups - 6700 mg caffeine. The number of test rats used was 144 males and 144 females; 41 males and 41 females served as controls. No bladder cancers or other serious changes were related to coffee in the 94 males and 99 females autopsied in the test group, nor in the 29 controls of each sex.

Gastric Ulcers

Giddings et al. (1109) in 1945 gave oral doses (stomach tube) of 75 mg/kg caffeine in either water or a 40% sucrose solution to groups of 7 to 10 weanling albino rats (34 total) daily for 8, 16, or 20 weeks. Littermated control rats were given equal doses of plain water. Only 3 rats in the 16-week groups and 3 in the 20-week group (given caffeine in water) had pathological stomach changes. The changes consisted of microscopic erosions, which were expected to heal. One animal had a small ulcer. In 3 other animals in these 2 groups some edema of the submucosa and diffuse acute inflammatory infiltration in the forestomach were found. These same changes were found in some of the control animals.

The authors tried to cause gastric ulcers in 26 cats - by giving them 75 mg caffeine alkaloid per kg body weight in a 2% aqueous solution by stomach tube daily for 21 days. Four controls were given the same amount of water similarly. The cats were given milk daily, free access to water and fed horsemeat ad. lib. with liver and beef kidney sometimes. No ulcers were produced in the 30 cats. A second study was done in which 20 cats were given 75 mg/kg caffeine-mineral oil-beeswax mixture i.m. daily for 21 days. Again, they found no ulcers. The investigators were able to produce ulcers in doses high enough to produce death - 150 mg/kg caffeine in beeswax and

oil i.m. daily. Four of the cats died in 4 days, one was sacrificed after 10 days, and the other 2 after 21 days. Three out of the 4 cats that died in the first 4 days had ulcers. Giddings et al. summarized that only enough caffeine which caused death produced ulcers in cats. This dose far exceeds that consumed by the normal human male, since 75 mg/kg daily is about equal to 50 cups of coffee per day. Giddings et al. concluded that caffeine-containing beverages do not contribute to gastric ulcers in the human.

In a previous study, Pfeiffer and Gass (2506) in 1955 found that large doses of caffeine produced stomach ulcers in rats. In this study they found that the intramural injection of 0.05 ml of caffeine (0.001 to 1.0 mg) in Ringer-Locke's solution into the submucosa of the glandular, everted rat stomach initiated gastric acid secretion. The 201 adult rats of both sexes were fasted for 24 hours prior to the surgery and were lightly anesthetized with sodium pentobarbital (35 mg/kg, i.p.). The test rats were vagotomized; controls were not. Fasted rats normally secrete gastric acid, whereas vagotomized rats normally do not have gastric secretion. Caffeine injected intramurally into vagotomized rats caused gastric acid secretion to occur. The author concluded that caffeine stimulated the parietal cells directly and may also have stimulated intramural, neural plexuses in the stomach. The authors concluded that the role of caffeine in ulcerogenesis is by hyper-stimulation of gastric acid secretion.

Reproduction

Thayer and Kensler (3220) reported in 1973 the results of exposing a population of CD-1 mice to continuous ingestion of caffeine for four generations. Three levels of caffeine were used: 4-5, 12-18 and 25-39 mg/kg/day in the drinking water. All treated animals of both sexes received caffeine continuously through pregnancy, lactation, growth and after weaning throughout the four generations. The first (P_1) generation consisted of 20 females and 10 males, each male being mated with 2 females; a 4-week premating period was observed. In the subsequent generations, each pair (one male and one female) were mated and allowed to produce two litters, one of which was raised to weaning and the other was sacrificed at birth for examination for birth defects.

F_1 offspring were selected for two types of mating: brother-sister matings and out-cross matings. F_2 pairs were selected to have no P_1 ancestor in common, and F_3 pairs had no F_1 parents in common but for most cases descended from common P_1 ancestors.

Gross pathologies and autopsies were made, particularly for stomach ulcers and bladder tumors as well as for teratologic abnormalities. No consistent, dose-related effects of caffeine on fertility, age at sexual maturity, mean litter size, weight of offspring at weaning, sex ratio or fetal abnormalities were observed. The authors suggest that these studies in the mouse "support the safety of caffeine in relatively high doses during reproduction".

Bachman et al. (141) in 1946 divided 100 weanling albino rats, into 25 groups of 2 males and 2 females each from the same litter; one male and one female per group were controls. The animals were given a Purina Dog Chow diet supplemented with green food and cod liver oil ad. lib. The sole fluid provided for the tests was a sweetened beverage containing caffeine. The test animals consumed 60 ml/day, which contained 12 mg caffeine, or an average of 40-50 mg/kg/day caffeine. The controls were given tap water, and they consumed about 30 ml/day. At 100 days of age the rats were mated (1 control male with 1 control female and 1 test male with 1 test female) and the mating pairs kept in separate cages. Each pair was sacrificed when the female did not become pregnant 3 months after the last litter. The total study was run over a 3 1/2 year period. No evidence of sterility due to daily ingestion of caffeine was found, as evidenced by the number of litters and offspring/litter. There were also no unusual histological changes in the testicles of the 23 test males and 15 controls studied.

Gilbert and Pistey (1112) in 1940 mated female, 200 g Holze rats, after which the spermatozoa in the vaginal smears were examined. The rats were then given 4 i.p. injections of caffeine per day at 6 hour intervals for 20 days. The dose levels were selected in order to simulate that taken in coffee containing 100 mg caffeine by human females, weighing 50 kg as follows:

Table 1. Dosage schedule of caffeine given to mated female rats

*Group**	*Caffeine†*	*Total daily dose*	*Daily caffeine equivalent as coffee/50 kg*
A	1 mg	4 mg	10 cups
B	2 mg	8 mg	20 cups
C	4 mg	16 mg	40 cups
D (control)	—	—	—

* Each group contained ten rats.
† Given intraperitoneally every 6 hr; the control group received 1 ml normal saline intraperitoneally every 6 hr.

The serum caffeine levels were highest 30 minutes after the injection. The results of reproductive parameters are summarized in Table 2:

Table 2. Effects of caffeine administration on the offspring of pregnant rats

Group	*Daily dose of caffeine (mg)*	*Average litter size*	*Average no. of resorptions*	*Average fetal weight (g)*	*Average placental weight (g)*
A	4	8	2·1	4·20	0·6
B	8	6	4·0	3·50	0·5
C	16	6	4·0	3·20	0·4
D	Control	10	1·2	4·60	0·7

The size of the litters in caffeine-treated groups was reduced by 20% in Group A and by 40% in Groups B and C. The average number of resorptions was twice as much as the control group in Group A and 4 times as much in B and C. The average fetal weights were significantly decreased in a dose-related way.. No teratogenic effects or abnormal placental changes were observed.

Behavioral Studies

Haldi et al. (1287) in 1947 gave 22 weanling rats 75 mg/kg caffeine in aqueous solution by stomach tube daily. Control litter-mates were given plain water daily. After 100 days, caffeine was withheld for 24 hours, after which the animals were given caffeine again and placed in activity cages for 220 daily observations. The caffeine stimulated spontaneous activity markedly during the 1st 30 minutes after the dosage. This effect was still manifest at the conclusion of the experiment 4 hours after the administration of caffeine. Long continued daily administration of caffeine had no permanent effect on basal activity. Caffeine has the same effect on activity when injected i.p.

Peters (2493) in 1967 observed hemorrhagic automutilation in albino Wistar rats intoxicated with caffeine. The caffeine was given orally by stomach tube - 185 mg/kg dissolved in 20 ml distilled water daily for 14 days. Control animals were given distilled water (20 ml/kg) only. The effects of various diets, starvation, the age and sex of the animal, and the presence or absence of other rats (1 or up to 10 rats per cage) on caffeine-induced self-mutilation were also studied. The number of animals per group varied from 5 to 54 in the 18 groups. The incidence of automutilation was increased by feeding the rats synthetic diets with large quantities of egg white powder, by starvation, and by isolation. The groups of male rats showed increased automutilation. Age had no effect on the incidence of the psychotic behavior. The presence of other rats allowed them to direct their aggression toward other rats, so that deaths

due to automutilation were fewer in aggregated cages.

Numerous psychological tests have been conducted to evaluate the effects of caffeine on the performance of physical and intellectual tasks and on mood and judgement in humans since the turn of the century. The review of Weiss and Laties (3462) in 1962 lists the following findings, some of which were based on fairly subjective criteria:

(1) Doses of about 500 mg caffeine, oral or i.v., significantly enhance the performance of physically exhausting work.

(2) Caffeine has little or no effect on reaction time.

(3) Caffeine may counteract decreased motor and arithmetic problem performance by alcohol.

(4) Caffeine impairs hand steadiness with a dose of 300 mg of the sodium benzoate salt or after 1 cup of coffee.

(5) Caffeine induces the tendency of subjects to respond earlier or more strongly in learning tests.

(6) Caffeine does not improve intellectual performance, but counteracts fatigue or boredom.

(7) The performance of arthmetic tasks are improved by caffeine (1 or 2 cups of coffee and a wide range of doses).

(8) After 180 or 360 mg caffeine, an increase in typing speed and decrease in number of errors was reported.

(9) Caffeine (420 mg) reduced symptoms of simulated high altitudes of 15,000 to 18,000 feet.

Lienert and Huber (1952) in 1966 gave a group of 50 male and female college students 10 standardized tests - one a speed test (dynamic factors); the others a speeded power test cognitive factors after the students were given a cup of strong coffee containing 0.3 g caffeine. A control group of 50 students were given no beverage. Tests which require speed were influenced significantly by coffee; mean performances were increased. Coffee also tended to reduce individual differences in certain intellectual abilities. The nonspeeded power tests were either unaffected or negatively affected by coffee.

Miscellaneous Studies

Marek (2065) in 1967 found that a single dose of 100 mg/kg caffeine, given orally or s.c., suppressed experimentally-induced edemas in white

rats, of both sexes, weighing 100 to 240 g. Caffeine had the greatest inhibitory effect on edemas produced by egg white and dextran, a lesser effect on edemas from kaolin and carrageenin, and the least effect on edemas from formaldehyde. The effect of caffeine on edemas was dose-related. The effect of caffeine pretreatment was unfavorable. Edemas were induced usually by injection under the palmar surface of the hind paw, but also into the animal's back. Caffeine was found to be anti-inflammatory, but did not influence granuloma formation around cotton pellets inserted under the dorsal skin of rats, when 100 mg/kg/day caffeine were given for 11 days. The author explained that the effect of caffeine on edemas was due to catecholamines released from the adrenal medulla.

Wolff and Varrone (3511) in 1969 fed male, 120 g Sprague-Dawley rats a Remington low iodine diet plus tap water ad lib for 24 days. The test rats were given 0.01 mg caffeine/g of low iodine diet during this time. Caffeine was found to be goitrogenic - thyroid weights increased with no significant decrease in serum PBI values, as shown in table 2.

TABLE 2. Comparisons of the goitrogenicity of various methyl xanthines

Treatment	Initial g	Final g	Thyroid weight ±SE mg/100 g	Serum PBI µg/100 ml	Serum methyl xanthines mM
Control (10)	112	244	9.3 ± 0.37	2.0	—
Theobromine (9) (3,7-Dimethylxanthine)	112	218	11.1 ± 0.64	1.8	0.24–0.34
Caffeine (10) (1,3,7-Trimethylxanthine)	114	222	14.6 ± 0.98	1.9	—
Aminophylline (9)	112	221	24.5 ± 1.5	1.0	0.36–0.53
Theophylline (10) (1,3-Dimethylxanthine)	114	233	24.3 ± 2.0	1.1	0.32–0.52

All drugs were fed at a concentration of 10 µmoles/g of low iodine diet for 24 days. The aminophylline concentration is per mole of theophylline contained therein. Numbers in parentheses refer to number rats/group. Serum PBI and methyl xanthine determination are means of 4-5 pools from 2 rats each

The authors stated that caffeine and other methyl xanthines inhibit mammalian cyclic 3',5'-nucleotide phosphodiesterase, including the thyroid enzyme. The goitrogenic effect of caffeine may be due to a higher level of 3',5'-AMP and an increased secretion of TSH. However, the mechanism is not clear, since at normal TSH levels, enlarged thyroids can still be produced. The possible reason for this was stated to be that caffeine increased the efficiency of thyroidal response to TSH.

Using a study with the double-blind design, Goldstein (1138) in 1964 found evidence to support the belief that caffeine prolongs the time needed to fall asleep in humans. Two hundred thirty healthy medical students (mostly male) were given capsules of lactose, pentobarbital (150 mg), or

caffeine (200 mg) before bedtime in one study, or decaffeinated coffee with caffeine added, or with lactose added as a placebo in the second study. In the latter study, tests were made to ensure that the subjects could not distinguish between real coffee and the placebo. A study was also done in which the subjects knew when they were taking caffeine. These subjects minimized the sleep-disturbing effects of caffeine (a "reverse placebo effect"). The more accustomed the subjects were to drinking coffee, the less it affected their sleep. Some of these subjects experienced a headache in the morning after abstaining from coffee for 18 hours.

Goldstein et al. (1144) in 1969 found that the physiological effects of caffeine in humans are different in those who abstain from coffee and those who are habituated to it. A placebo-controlled double-blind experiment was done in which either 150 or 300 mg caffeine or lactose were added to decaffeinated coffee and ingested as the morning coffee. There were 18 abstainers and 38 drinkers of 5 or more cups of coffee daily who participated in the experiments. All of the subjects were housewives in a Stanford University housing unit for married students. The women were given the test cups of coffee for 9 consecutive mornings, and each treatment was given 3 times. The subjects were asked for subjective evaluations of how they felt in 11 areas, such as the presence of headache, upset stomach, nervousness, etc. Various caffeine-withdrawal symptoms (12 to 16 hours after the last dose) were experienced by women who normally drank coffee and received the placebo (which could not be distinguished from the caffeinated coffee). Positive effects were felt by coffee-drinkers after ingesting the caffeinated coffee, and negative effects were felt by those who normally abstained. It was also found that coffee-drinkers felt better after the higher dose of caffeine, and abstainers felt worse.

Several instances of visual disorder following excessive coffee (and tea) consumption were reported in 1950 by Schulte (2882) who related a personal reaction to drinking a dozen or more cups of strong coffee or tea over three days time with subsequent entroptic scotomas and hemianopsia, accompanied by severe headaches. A fellow physician suffered a similar experience after several cups of strong coffee which caused the momentary loss of vision in both eyes and intense, long-lasting headaches. The author's explanation for the visual phenomena lay in the relative overdosage of caffeine producing spasms in the blood vessels of the brain, acting as both a vasodilatory and constrictor.

Using 3 human subjects, Diamond and Cole (761) in 1970 found that the oral administration of 1.5 to 3.0 grains of caffeine (97.2 to 194.4 mg) caused a dose-related decrease in visual threshold. In other words, caffeine was shown to enhance absolute visual sensitivity (see Figure 2 and 3).

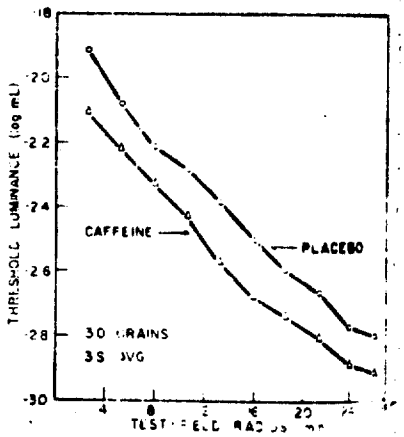


Fig. 3. Threshold in log mL as a function of test-field radius for three grains of caffeine vs no caffeine (placebo condition)

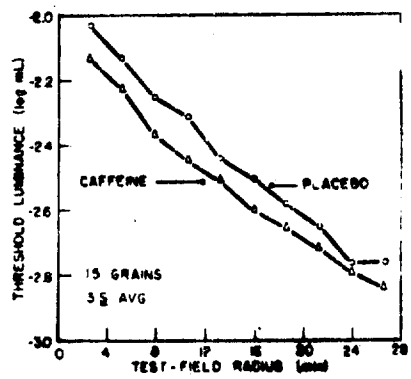


Fig. 2. Threshold in log mL as a function of test-field radius for 1½ grains of caffeine vs no caffeine (placebo condition).

Dreisbach et al. (807) in 1943 gave caffeine capsules as the citrate or sodium benzoate salt in increasing daily doses, from 120 to 780 mg per day, to 20 male and 2 female students for 6 or 7 days. On the 7th or 8th day, placebos were substituted without the subjects' knowing. No other caffeine sources were consumed by the subjects during the experiment. This sudden withdrawal of caffeine resulted in severe headaches in 55% of the 38 trials. In 29% of the trials, the headache was much less severe. No headache occurred in 16% of the trials. Blood samples showed that a decrease in serum calcium and an increase in serum phosphorus were present with the headache.

Fujii et al. (1047) in 1972 conducted experiments on the relationship of caffeine and the performance of race horses. Preliminary tests with three thoroughbreds (weights approximately 420-500 kg) established that 20% sodium benzoate caffeine injections of 2.5 g were ineffective, and a dose of 5 g produced positive results (dimunition of drowsy signs, slight changes in heart beat and behavior, but no indications of hyperkinesia or excitation. Running tests decreased lap time due to an enhancement in the impulse to run; heart beat measurements showed an increased rate, with intermittent arrhythmic signs. The authors recommended that dope should be prohibited for the physical well-being of the horse.

Biochemical Aspects

I. Breakdown

No Information Found

II. Absorption - Distribution

Burg and Werner (468) reported on the distribution of caffeine and its metabolites in the mouse in 1972; a related study by Burg and Stein (467) in the same journal described the excretion of caffeine and metabolites in the mouse and is abstracted in the section on Metabolism and Excretion in this monograph. The techniques developed for the identification of caffeine metabolites were used in both studies.

Male CD-1 mice weighing about 30 g were used in the experiment. Doubly-labeled radioactive caffeine (C^{14} and H^{3} isotopes) was orally intubated in either 5 or 25 mg/kg doses to groups ot 3 animals for each dose and for each period of sacrifice of the animals at 0.08, 0.5, 1, 3, 8 and 24 hours after dosing. Brain, heart, kidneys, liver, lungs, spleen and testes were immediately removed; muscle and blood samples were also taken. Some mice were given caffeine in the drinking water over a period of 8 months since weaning before dosing with the radioactive caffeine; twenty-four after dosing, the animals were quick-frozen for microtomy and radioautography.

The various organs were homogenized and samples were counted for radioactivity in a scintillation spectrometer. Other organ tissue homogenates were purified and the radioactive metabolites identified by paper chromatography in multiple chromatographic systems and located in the chromatograms by a radiochromatogram scanner. Quantitation was effected by the use of a compensating polar planimeter.

The concentrations of caffeine, its major metabolites and unidentified radioactive species are presented in the following tables:

TABLE 1. MAJOR ^{14}C-COMPOUNDS IN THE ORGANS OF THE MOUSE WITHIN 1 hr AFTER A 25-mg/kg DOSE OF [^{3}H,^{14}C]CAFFEINE

Compounds	Per cent of administered ^{14}C-radioactivity in									
	Brain (0·40 g)*	Heart (0·15 g)	Kidneys (0·47 g)	Liver (1·70 g)	Lungs (0·23 g)	Spleen (0·17 g)	Testes (0·22 g)	Muscle (12·9 g)	Blood plasma (1·46 ml)	Erythrocytes (0·87 ml)
At 5 min										
Total radioactivity	0·63	0·31	1·18	7·2	0·56	0·48	0·14	13·1	4·1	0·52
Extractable radioactivity	0·65	0·31	1·17	6·7	0·58	0·50	0·14	13·1	4·1	
Total acids	0·01	0·00	0·02	0·06	0·00	0·01	0·00	0·66	0·06	
Total non-acids	0·58	0·28	1·20	5·5	0·48	0·45	0·13	12·5	2·82	
Caffeine	0·58	0·28	1·20	5·5	0·48	0·45			2·13	
At 30 min										
Total radioactivity	0·94	0·42	1·54	5·1	0·61	0·46	0·67	29·9	4·2	0·69
Extractable radioactivity	0·97	0·47	1·49	5·8	0·65	0·49	0·67	29·4	3·5	
Total acids	0·01	0·01	0·04	0·25	0·01	0·01	0·01	0·49	0·18	
1-Methyluric				0·12						
Total non-acids	0·88	0·37	1·37	5·5	0·64	0·36	0·54	30·9	2·94	
Caffeine	0·65	0·27	1·01	4·8	0·52	0·28	0·54	23·5	2·07	
1,7-CH_3-xanthine	0·23	0·10	0·35	0·65	0·12	0·08			0·69	
At 1 hr										
Total radioactivity	0·87	0·40	2·02	5·9	0·56	0·43	0·95	35·8	4·8	0·62
Extractable radioactivity	0·85	0·38	1·89	5·8	0·58	0·52	1·21	3·52		
Total acids	0·01	0·01	0·11	0·41	0·01	0·02	0·14	0·00		
1-Methyluric			0·04	0·24	0·00	0·00				
Total non-acids	0·70	0·33	1·69	4·7	0·51	0·39	0·60	34·0		
Caffeine	0·61	0·26	0·98	2·7	0·38	0·25	0·38	22·7		
1,7-CH_3-xanthine	0·09	0·07	0·49	1·6	0·04	0·14	0·22			

* The average weight of each organ is given in parentheses.

TABLE 2. MAJOR ^{14}C-COMPOUNDS IN THE ORGANS OF THE MOUSE 3 hr AFTER A 25-mg/kg DOSE OF [^{3}H,^{14}C]CAFFEINE

Compounds	Per cent administered ^{14}C-radioactivity in									
	Brain (0·37 g)*	Heart (0·15 g)	Kidneys (0·47 g)	Liver (1·50 g)	Lungs (0·23 g)	Spleen (0·16 g)	Testes (0·25 g)	Muscle (12·9 g)	Blood plasma (1·46 ml)	Erythrocytes (0·87 ml)
At 3 hr										
Total radioactivity	0·32	0·19	1·82	3·9	0·30	0·26	0·27	13·4	2·07	0·42
Extractable radioactivity	0·35	0·19	1·65	3·6	0·28	0·21	0·26	16·9	2·07	
Total acids	0·01	0·01	0·24	0·53	0·02	0·02	0·02	1·17	0·33	
1-Methyluric			0·11	0·36	0·00	0·01			0·15	
Total non-acids	0·31	0·15	1·42	2·4	0·19	0·17	0·21	13·4	1·44	
Caffeine	0·22	0·08	0·47	1·14	0·12	0·10	0·12		0·69	
1,7-CH_3-xanthine	0·09	0·06	0·53	0·90	0·08	0·08	0·09		0·42	
At 8 hr										
Total radioactivity	0·04	0·03	0·33	1·15	0·10	0·08	0·14	6·6	0·60	
Extractable radioactivity	0·06	0·03	0·26	0·86	0·08	0·05	0·16	6·6	0·57	
Total acids		0·00	0·03	0·19	0·01	0·02	0·03			
1-Methyluric			0·02	0·17						
Total non-acids		0·02	0·19	0·44	0·03	0·03	0·09			
At 24 hr										
Total radioactivity	0·03	0·02	0·22	0·60	0·07	0·05	0·03	1·47	0·24	0·07
Extractable radioactivity	0·06	0·01	0·12	0·28	0·07	0·03	0·05	1·47	0·24	
Total acids		0·00			0·00	0·01	0·00			
Total non-acids		0·01			0·01	0·02	0·01			

* The average weight of each organ is given in parentheses.

TABLE 3. MAJOR ^{14}C-COMPOUNDS IN THE ORGANS OF THE MOUSE AFTER A 5-mg/kg DOSE OF [^{3}H,^{14}C]CAFFEINE

Compounds	Per cent administered ^{14}C-radioactivity in									
	Brain (0·37 g)*	Heart (0·15 g)	Kidneys (0·47 g)	Liver (1·77 g)	Lungs (0·26 g)	Spleen (0·17 g)	Testes (0·24 g)	Muscle (12·9 g)	Blood plasma (1·46 ml)	Erythrocytes (0·87 ml)
At 5 min										
Total radioactivity	0·57	0·31	1·06	6·6	0·65	0·60	0·17	21·2	3·54	0·60
Extractable radioactivity	0·56	0·28	1·06	6·7	0·44	0·64	0·17	20·4	3·46	
Total acids	0·01	0·01	0·02	0·10	0·01	0·00	0·00	0·29	0·15	
Total non-acids	0·48	0·23	1·11	5·7	0·41	0·53	0·14	17·4	2·54	
Caffeine	0·41	0·23	1·01	5·7	0·41	0·53		17·4	2·54	
1,7-CH_3-xanthine			0·10							
At 1 hr										
Total radioactivity	0·58	0·29	2·40	6·9	0·73	0·29	0·32	23·8	4·52	0·58
Extractable radioactivity	0·58	0·36	2·38	6·4	0·47	0·32	0·36	23·4	4·43	
Total acids	0·01	0·02	0·19	0·62	0·20	0·01	0·02	0·73	0·63	
1-Methyluric					0·02					
Total non-acids	0·54	0·28	2·24	5·4	0·36	0·27	0·31	20·6	3·09	
Caffeine	0·25	0·14	0·85	1·63	0·19	0·16	0·18	12·7	0·86	
1,7-CH_3-xanthine	0·10	0·14	1·27	1·50	0·17	0·11	0·13	8·0	1·06	
At 8 hr										
Total radioactivity	0·04	0·04	0·35	2·0	0·20	0·19	0·08	3·6	0·60	0·10
Extractable radioactivity	0·09	0·03	0·24	1·2	0·11	0·05	0·09	5·1	0·40	
Total acids	0·01	0·01	0·03	0·18	0·01	0·00	0·01	0·55		
1-Methyluric										
Total non-acids	0·04	0·02	0·18	0·76	0·03	0·03	0·06	2·3		
1,7-CH_3-xanthine								2·3		

* The average weight of each organ is given in parentheses.

Within 5 minutes of dosing, the caffeine radioactivity rapidly entered organs and tissues, as caffeine; very little radioactivity was observed in the plasma as metabolites. At 30 minutes, the caffeine concentrations in the organs had increased slightly; the major metabolite at that time was 1,7-dimethylxanthine. One hour after dosing, the caffeine concentrations in the organs had fallen to about half the earlier concentrations, and the major metabolite was still 1,7-dimethylxanthine; at later time periods, caffeine, 1,7-dimethylxanthine and 1-methyluric acid were present in liver, lungs, kidneys, testes and plasma. By 8 hours, and at 24 hours the level of radioactivity had fallen so low that identification of metabolites was difficult. Further analyses indicated that a barrier in brain and testes prevented accumulation of caffeine in those organs; liver, spleen and perhaps kidney actively remove caffeine from the plasma. The half-life of caffeine in all organs investigated was less than 3 hours, due to rapid metabolism and excretion of caffeine metabolites.

Sant'Ambroglo et al. (2795) in 1964 studied the time courses of plasma levels of caffeine in 5 male human subjects given caffeine orally or intramuscularly, and in 3 humans and 3 dogs given caffeine intravenously. Doses varied from 6 to 9 mg/kg body weight. Following administration of the caffeine (as alkaloid in oral doses; as caffeine - sodium benzoate in intramuscular and intravenous doses) blood samples were taken usually at intervals of 15, 30, 60, 90 and 150 minutes after oral and intramuscular administration, and of 2, 5, 10, 20, 40 and 60 minutes after intravenous injection.

In all 5 experiments in which the caffeine was given orally, the plasma levels of caffeine peaked at 30 minutes; in those in which intramuscular injection was the method of giving the caffeine, plasma levels peaked at 60 minutes. The following figure demonstrated the results:

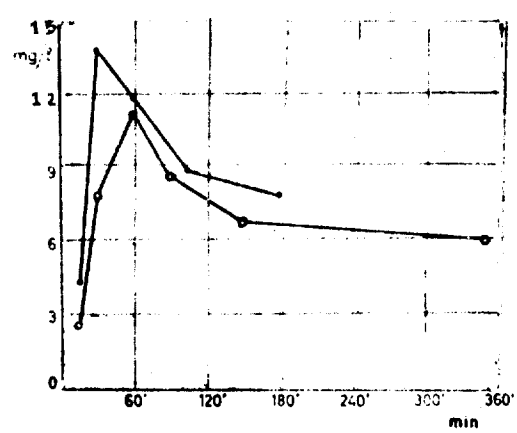


FIG. 1

Plasma levels of caffeine after oral (●) and intramuscular (○) administration; 0.5 g of caffeine was given in both the two experiments to the same subject weighing 80 kg.

In the intravenous injections, caffeine diffusion through the vascular walls is very rapid; the half reaction time is about 1.5 minutes. The rate of biotransformation or metabolism was determined to have an average half reaction time of a few minutes over 3 hours.

Axelrod and Reichenthal (134) in 1953 studied the fate of caffeine in man. Plasma levels of caffeine were compared after oral and intravenous administration of 7 mg/kg of caffeine in three men. After oral administration, peak plasma levels of about 10 mg/l occurred in about one hour after which levels closely approximated those following the intravenous administration. The data indicated rapid and essentially complete absorption from the gastrointestinal tract.

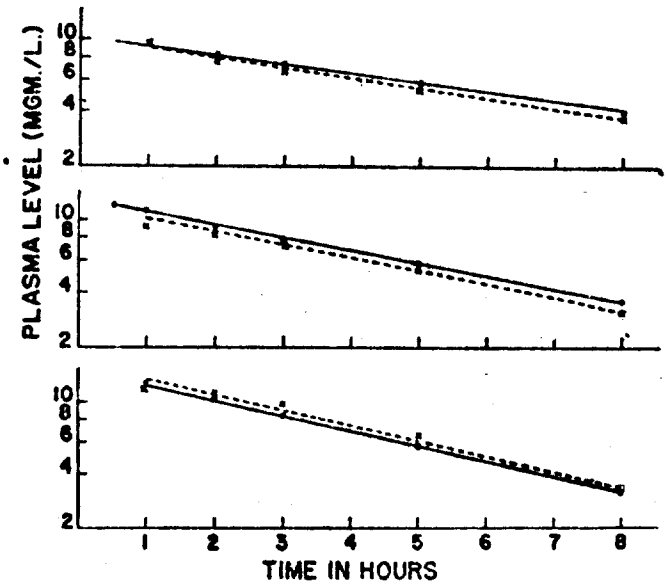


FIG. 1. Plasma levels of caffeine after the oral (solid line) and intravenous (dashed line) administration of 7 mgm. per kgm. of caffeine to three subjects.

A dose of 500 mg of caffeine was given intravenously to each of three men and urine was collected for the subsequent 24 hours. Only 0.5 to 1.5 percent was excreted unchanged in the urine. In another study 12 men were given 7 mg/kg of caffeine intravenously and plasma levels were measured at various time intervals. The time required for the plasma level to fall to half its value was found to be fairly uniform from subject to subject, averaging 3.5 hours and ranging from 2.5 to 4.5 hours (12 to 22 percent disappearance per hour). In dogs following the intravenous administration of 4 mg/kg of caffeine the biologic half-life averaged 5 hours, a value about the same as that found for man.

Plasma levels of caffeine were measured in 5 human subjects who had

consumed eight cups of coffee over a period of seven hours. Considerable amounts of caffeine accumulated in the body but this had largely disappeared by the following morning.

TABLE 3

Plasma levels of caffeine after coffee drinking

Two cups of coffee taken at 8:00 a.m., 12 noon, 3:00 p.m., and 6:00 p.m. Blood samples were drawn at 8:00 a.m. (B_0), 9:00 a.m. (B_1), 1:00 p.m. (B_2), 7:00 p.m. (B_3), and the following morning at 8:00 a.m. (B_4). No caffeine containing beverages were taken 24 hours prior to the experiment or during the interval between B_3 and B_4.

SUBJECT	PLASMA CAFFEINE CONCENTRATION MGM./L.				
	B_0	B_1	B_2	B_3	B_4
1	0.4	2.7	3.5	4.8	0.3
2	0.9	1.5	1.9	4.0	0.2
3	0.5	0.7	1.3	4.2	0.6
4	0.4	1.9	2.8	3.9	0.7
5	0.03	1.6	2.1	3.6	0.5

In a dog study the author administered 84 mg/kg of caffeine intravenously and examined the tissues 3 hours after the administration of the caffeine. Caffeine was distributed in the various tissues in approximate proportion to their water content. Caffeine passed rapidly into the brain.

TABLE 2

The distribution of caffeine in dog

The dog received 84 mgm. per kgm. of caffeine intravenously. The tissues were examined 3 hours after the administration of the drug.

TISSUE	CAFFEINE IN TISSUE WATER *mgm./kgm.*	RATIO: Tissue water caffeine / Plasma water caffeine
Plasma	82.7	1.0
Red blood cells	83.0	1.0
Cerebrospinal fluid	78.2	0.95
Liver	91.7	1.11
Lung	71.5	0.87
Heart	77.0	0.93
Muscle	71.0	0.86
Kidney	82.1	0.99
Spleen	73.2	0.89
Brain	77.2	0.93

The mutagenicity of caffeine observed in experiments with bacteria, fungi and the fruit fly Drosophila has implications involving higher organisms, including man - due to the similarities in all life-forms of the mechanism of genetic replication. In man, the crucial or hazardous periods would involve the active reproductive years of adults, and the fetal life between 6-8 weeks, or the period of early organogenesis and segregation of the germ cells comprising testes and ovaries. A mutagen, however, must have access to germinal tissue, and Goldstein and Warren

(1141) conducted experiments in 1961 which demonstrated that caffeine equilibrates freely between plasma and tissue water of human testis and ovary and also between maternal plasma and the 7-8 week fetus.

Gonads were obtained as surgical specimens; testes from orchidectomy patients and ovaries from oophorectomy patients undergoing surgical treatment for prostate and breast cancers. Fetuses were from therapeutic abortions performed during the 7th-8th weeks of gestation. Controls were found to be unnecessary. For ovarian studies, 1 g caffeine-sodium benzoate was given intravenously and 15-20 minutes before removal of the ovary; in testes and fetus experiments, the same dose of caffeine-sodium benzoate was administered 30 minutes prior to surgical removal of testes and fetus. Blood samples were taken simultaneously to removal of relevant tissues. Caffeine analyses were performed by a modification of Axelrod and Reichenthal (see paper in this section of monograph). The results are shown in the following 3 tables which are self-explanatory:

TABLE 1. Caffeine Content of Ovary

Patient	Age	Equilibration time* (min)	Caffeine concentration (µg/ml)	
			Ovary#	Plasma
K	47	20	26.5	30.8
N	43	15	23.0	21.5

* After intravenous administration
\# The caffeine concentration is expressed in µg per ml of tissue water assumed to be 70 percent of wet-weight.

TABLE 2. Caffeine Content of Testis

Patient	Age	Equilibration time* (min)	Caffeine concentration (µg/ml)		
			Right testis#	Left testis#	Plasma
R	60	75	10.9	10.3	9.8
S	86	120	9.0	8.9	9.8

* After intramuscular administration. The time given includes the absorption time.
\# The seminiferous tubule mass was dissected free of all accessory tissues. The caffeine concentration is expressed in µg per ml of tissue water, assumed to be 70 percent of wet-weight.

TABLE 3. Caffeine Content of Fetus

Patient	Weight of fetus (g)	Equilibration time (min)	Caffeine concentration (µg/ml)	
			Fetus#	Maternal Plasma
H	1.72	50 (intramuscular injection)	1.9	3.5
L	2.73	40 (intravenous injection)	9.9	10.2

* The gestational age of both fetuses was 7-8 weeks. The fetus from patient H was obtained as fragments from curettage, that from patient L intact by hysterectomy. Fetal caffeine concentration is expressed in µg per ml of tissue water, assumed to be 70 percent of wet-weight.

The authors concluded that the germ cells of regular coffee or tea drinkers are bathed in a caffeine solution estimated to be equivalent to a continuous exposure of about 1 microgram per milliliter. Fetal gonad cells in the pregnant woman would also be exposed to similar concentrations of caffeine. "Whether, and under what conditions, such chronic exposure of the human germ line to caffeine may constitute a genetic hazard is at present entirely unknown."

An abstract of a paper given at the Fourth Annual Meeting of Toxicology of Applied Pharmacology in 1965 by Parish et al. (2461) presents a study of the distribution in body tissues of caffeine involved in a suicidal case. No indication of the dose of caffeine involved was given. Tissues were obtained and caffeine concentrations determined by u.v. and infra-red spectrometry, spot tests and thin-layer chromatography. Stomach tissues showed concentrations of 150.66 mg/100 g tissue; liver, 32.90; kidney, 12.96 and brain, 7.47 mg/100 g tissue. Comparative studies with 10 male rats, weighing about 200 g, given orally 1 g/kg caffeine, were made. Tissues obtained at autopsy were analyzed for caffeine. The distribution of caffeine was in the same sequential order in the rat as in the human tissue.

III. Metabolism and Excretion

The extensive metabolism of caffeine has led to disparate results by various investigators and to a general lack of detailed data. Burg and Stein (467) in 1972 selected the mouse and radioactively labeled caffeine (C^{14}-caffeine-1-methyl and generally-labeled tritium caffeine) for studies of the urinary excretion of caffeine and its metabolites. The labeled compounds were diluted with caffeine and used together in a ratio of 1 microcurie C^{14} to 50 microcuries H^3 in the experiments. Male CD-1 mice weighing about 30 g were given single oral doses of intubation of either 5 or 25 mg/kg of labeled caffeine with radioactivity of 250 microcuries per ml tritium, 5 microcuries per ml C^{14} (the caffeine solutions were of strengths 0.5 or 2.5 mg/ml). One group of mice were tested for differential metabolism of a single dose of the labeled caffeine by having received over a period from weaning to 4 months, 4.1 or 25.2 mg/kg/day of caffeine in the drinking water before being tested with the labeled caffeine. Following the oral administration of labeled caffeine, air samples, urine and feces were periodically collected for up to 32 hours for assay of radioactivity by scintillation spectrometer. The C^{14} was located by radio-chromatography and the scintillation spectrometer. Standards used in the experiments were either commercially obtained or synthesized biologically.

The results following a single dose of radio-labeled caffeine in both naive animals (not pre-treated with caffeine), and those chronically given caffeine since weaning, are shown in the following figure:

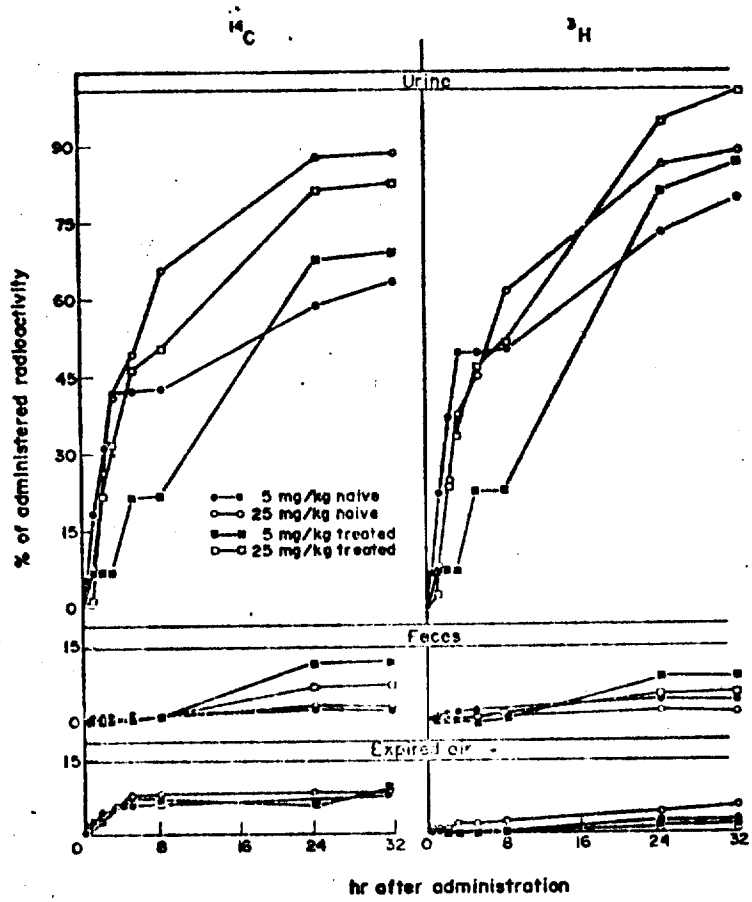


FIG. 1. Excretion of radioactivity after the administration of a single dose of [^{3}H,^{14}C]caffeine, p.o. Naive animals had not previously been exposed to caffeine. Treated animals had received an average of either 4·1 or 25·2 mg/kg/day caffeine since weaning.

B.P. 21/7—B

Little difference between doses of 5 or 25 mg/kg of labeled caffeine was observed. Urinary tritium concentration exceeds that of expired air and feces, presumably due to equilibration with body water and excretion as H_2^3O regardless of intermediary metabolism. More C^{14} than H^3 was recovered in the expired air, probably due to $C^{14}O_2$ resulting from the metabolism of the 1-methyl group of caffeine after demethylation. Only the fecal route showed significant difference in the disposition of the labeled caffeine between pretreated and "naive" animals; the excretion of the radioactive tracers in the pretreated mice was twice to more than 4 times that of the naive mice. The fecal route, however, did not appear to be a major excretory pathway for caffeine metabolites in the mouse; the caffeine itself was almost entirely absorbed from the gastrointestinal tract and did not pass directly into the feces.

Many radioactive metabolites appeared in the urine; volatile components were directly determined by scintillation counting. The non-volatile urinary metabolites were determined by multiple chromatography. A summary of the findings is presented in the following figure:

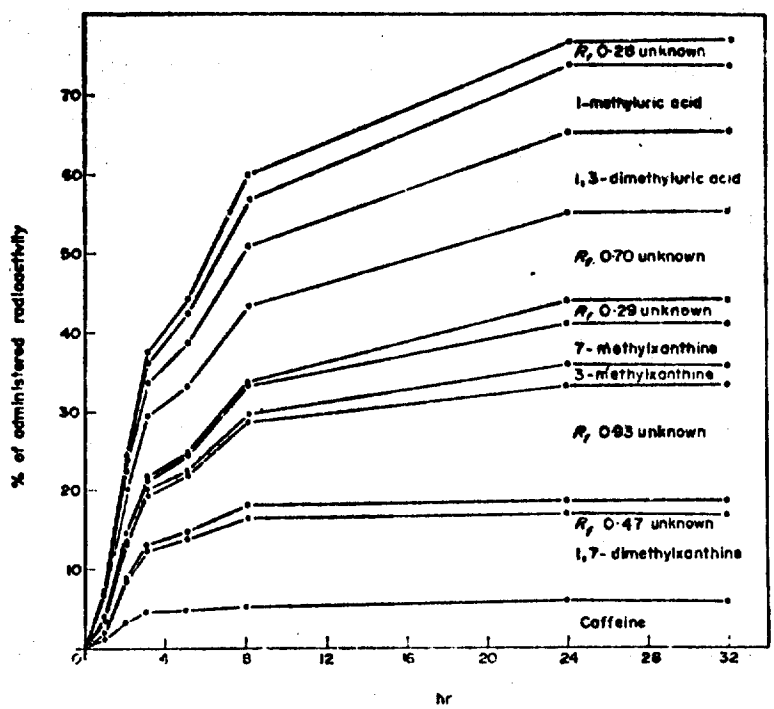


FIG. 4. Major radioactive metabolites in the urine of the mouse after the administration of 25 mg/kg [^{3}H,^{14}C]caffeine, p.o. Urine of three male CD-1 mice was pooled at each time period. The identity and quantity of metabolites were determined by multiple chromatography as described in the text. Data are presented as summated cumulative excreted per cents of administered radioactivity.

Of the total radioactivity of the administered caffeine, 64-90% was recovered in the urine. The major identifiable urinary metabolites were 1,7-dimethylxanthine; 3-methylxanthine; 7-methylxanthine; 1,3-dimethyluric acid and 1-methyluric acid. Only 3-6% of the caffeine given

orally appeared in the urine; excretion of the metabolites was rapid, about 80% within 8 hours of dosing with the 25 mg/kg radio-labeled caffeine.

The metabolism of the methylated xanthines, with their marked stimulatory and diuretic actions as observed from the use of coffee, tea and cocoa, has been extensively investigated. The appearance of monomethylxanthine in the urine of human and experimental animals has indicated that the di- and tri-methylxanthines are at least partially demethylated during metabolism. The possibility that some portion of these metabolites are further converted to uric acid was investigated about 30 years ago by Buchanan et al. (437). Earlier studies had suggested that no increased urinary excretion of uric acid followed ingestion by human subjects of the three beverages noted above; the authors attributed this general finding to inaccuracies of the then-available (circa 1900) gravimetric and titrimetric methods for determination of uric acid. Improved colorimetric procedures for analyses for uric acid during the early 1900's reversed the point of view; investigations demonstrated that uric acid excretion was increased, but presumably not due to direct oxidation of methylxanthines, but rather to a stimulation of general metabolism. The increased uric acid excretion was observed following caffeine and theophylline (coffee and tea) ingestion, but not from theobromine (cocoa).

An enzymatic procedure (a uricase application) which determined uric acid in the presence of its methylated derivatives was developed by the authors and applied experimentally to studies by five different individuals given caffeine, theophylline and theobromine with determinations of subsequent uric acid excretion. Using the uricase enzymatic procedure showed that oral administration of caffeine, theophylline, or theobromine has little effect on the excretion of true uric acid over 24-hour periods. The typical results of the studies are shown by the data presented for the subject O.H.B.: Table I, uric acid excretion for all three methylated xanthines; Figure 1, caffeine and theophylline; Table III, the 24-hour values summarized from data of Figure 1.

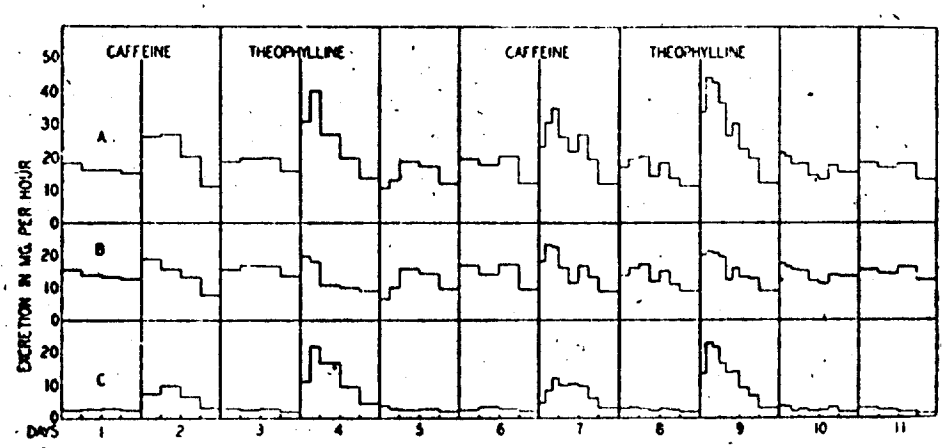


FIG. 1. Uric acid excretion following the ingestion of caffeine and theophylline by subject O. H. B. 500 mg. of caffeine were taken on the 2nd and 7th days and 500 mg. of theophylline on the 4th and 9th days. Each small division on the abscissa represents 6 hours. *A*, total phosphotungstic acid-reducing materials; *B*, true uric acid; *C*, non-uric acid reducing materials.

TABLE I

Effect of Ingestion of Methylated Xanthines on Uric Acid Excretion

Subject, O. H. B.; age, 28; weight, 130 pounds. All values are expressed as mg. excreted in 24 hours.

Date	Uric acid by uricase method			Uric acid by silver pptn.	Diet
	Total color*	Residual color*	True uric acid		
1943					
Mar. 29	412	42	370		Low purine
" 30	442	49	393	341	" "
" 31	450	43	407	375	" "
Apr. 1	719	302	417	621	1 gm. caffeine
" 2	889	454	435	780	1 " "
" 3	789	409	380	666	1 " "
" 4	497	114	383	439	Low purine
" 5	429	49	380	377	" "
" 6	370	40	330	290	" "
June 9	370	34	336	352	" "
" 10	454	44	410	419	" "
" 11	432	42	390	391	" "
" 12	850	454	396	549	1 gm. theophylline
" 13	897	509	388	590	1 " "
" 14	910	543	367	635	1 " "
" 15	537	212	325	366	Low purine
" 16	488	60	427	424	" "
" 17	415	61	354	364	" "
1944					
Mar. 9	406	34	372		" "
" 10	392	34	358		" "
" 11	358	34	324		" "
" 12	388	53	334	347	1 gm. theobromine
" 13	344	55	289	277	1 " "
" 14	401	57	344	351	1 " "
" 15	414	49	365		Low purine
" 16	444	55	389	396	" "

* Expressed in terms of uric acid.

TABLE III

*Effect of Ingestion of Caffeine and Theophylline on Uric Acid Excretion**

Subject, O.H.B.; age, 29; weight, 130 pounds. All values are expressed as mg. excreted in 24 hours.

Date	Total reducing materials†	Non-uric acid reducing materials†	True uric acid	Diet
Apr., 1944				
19	397	63	334	Low purine
20	509	173	336	500 mg. caffeine
21	442	63	379	Low purine
22	576	283	293	500 mg. theophylline
23	357	67	290	Low purine
24	415	68	347	" "
25	532	179	353	500 mg. caffeine
26	375	66	309	Low purine
27	626	272	354	500 mg. theophylline
28	399	62	337	Low purine
29	395	49	346	" "

* Data from Fig. 1 summarized for 24 hour periods.

† Measured in terms of uric acid.

The authors suggest that the definite increase in the excretion of phosphotungstic acid-reducing materials which remain unaffected by the uricase procedure may be due to 1-methyluric acid, 3-methyluric acid, or 1,3-dimethyluric acid formed by the oxidation and partial demethylation of the methylated xanthines.

Chromatography and urine analyses were employed by Weinfeld and Christman (3460) some 20 years ago to identify methyluric acids in urines of humans, rat and rabbit following ingestion of caffeine (and theophylline). A total dose of 1 g caffeine given the human male subject resulted in the conclusion that 1-methyluric acid was an important metabolite in the human body, with evidence that some 1,3-dimethyluric acid may also be a metabolite. No evidence of 3-methyluric acid was found in the human experimental urine. Similar results were found in the same human subject given 0.7 g theophylline. Experiments with albino rats and an albino rabbit given both caffeine and theophylline supported the results, in general, found in man.

Cornish and Christman (633) followed up the foregoing studies by Weinfeld and Christman 4 years later using several human subjects, given 1 g doses of theobromine, theophylline, or caffeine, and analysing urine by chromatography and silver salt precipitation procedures for methylxanthine and methyluric acids. The following table summarizes the findings:

TABLE II

Methylxanthine and Methyluric Acid Excretion during 48 Hour Period after Ingestion of 1 Gm. of Designated Methylxanthine

All the values are expressed as mg. of the administered compound required to give the excretory product.

Compound excreted	Compound ingested					
	Theobromine		Theophylline		Caffeine	
	Subject H. C.	Subject F. M.	Subject H. C.	Subject F. M.	Subject H. C.	Subject F. M.
Theobromine (3,7-dimethylxanthine)	124	117				
3-Methylxanthine	182	215	155	111		
7-Methylxanthine	280	281			90	40
7-Methyluric acid	42	36				
Theophylline (1,3-dimethylxanthine)			87	111		
1-Methyluric acid			186	186	254	304
1,3-Dimethyluric acid			382	318	142	46
Caffeine (1,3,7-trimethylxanthine)					11	12
1-Methylxanthine					182	199
1,7-Dimethylxanthine					74	19
Total	628	649	810	726	758	620

The work of Buchanan et al. (437) using the uricase enzymatic procedure for uric acid determination is cited by Cornish and Christman (see in this section of monograph) who found no true uric acid increase following ingestion of the three methylxanthines. The authors postulate a probable scheme for the metabolic pathways of the xanthines in man, shown as follows:

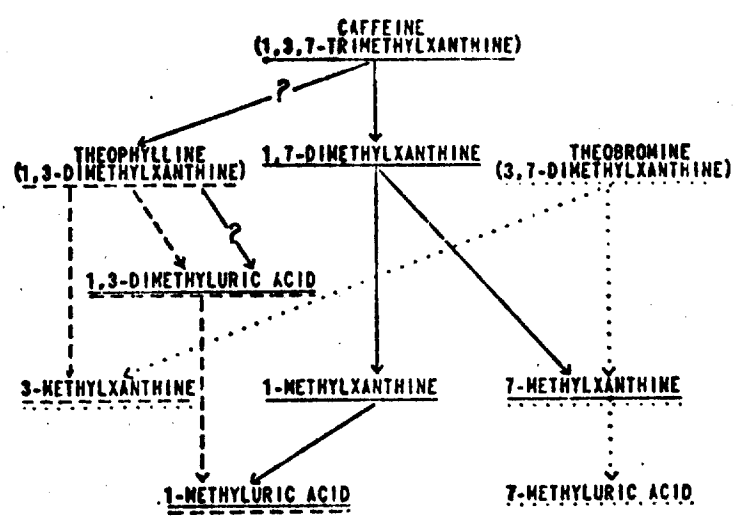


FIG. 1. Compounds excreted by man after the ingestion of caffeine (solid line) theophylline (dashed line), and theobromine (dotted line).

As recently as 1969, Warren (3442) remarks in her report that despite the enormous quantities of xanthine alkaloids consumed world-wide in a variety of beverages, "remarkably little is known about their metabolism in man". As a preliminary to further studies of caffeine metabolism in man, Warren attempted the separation and identification of caffeine and its metabolites in human blood. Numerous solvent systems for separation of caffeine and dimethylxanthines in plasma or red cells were tried. A 2-stage system for thin-layer chromatographic separation was devised and applied to blood samples from a series of human volunteers with the following results:

(1) Habitual consumers of beverages containing caffeine require about 7 days of abstention from them before caffeine completely disappears from their blood extracts.

(2) In such "decaffeinated" subjects administration of 500 mg caffeine orally leads to the appearance of caffeine and paraxanthine in both red cells and plasma within 3 hours.

(3) Caffeine and paraxanthine then disappear from the blood extracts within 24 hours.

From these findings it appeared to the author that the first step in caffeine metabolism in man is the removal of the 3-methyl group and formation of 1,7-dimethylxanthine, or paraxanthine. The marked difference in time required to "decaffeinate" habitual versus decaffeinated subjects is not understood.

IV. Effects on Enzymes and Other Biochemical Parameters

In Heyden's review (1396) in 1969 of the effect of coffee on lipid metabolism, numerous studies have shown that the administration of caffeine-orally as coffee or coca cola, or as caffeine i.v. or i.m. - temporarily raises the free fatty acid level in the plasma. A significant increase was observed to occur within 3 to 4 hours. The numerous studies on the effect of coffee on serum lipids and lipoprotein levels had conflicting results. The author tends to believe that there is no evidence to support the elevation of cholesterol levels, which can lead to heart disease, by caffeine in humans or laboratory animals.

The extreme sensitivity of mice with hereditary-obese hyperglycemic syndrome to caffeine toxicity, reported by Kuftinec and Mayer (1828) in 1964, has been in part described in Biology I Section of this monograph (Toxicity). Additional studies by the authors included the effect of caffeine on blood glucose, glucose and insulin tolerance after caffeine treatment, and histologic studies.

A group of 60 obese mice received 2 mg/0.2 ml H_2O per animal and 40 lean mice were injected with 5 mg/0.3 ml H_2O per mouse, in studies of caffeine influence on blood glucose. Thirty animals of each type received 0.3 ml H_2O only and served as controls. An ultramicro modification of the

Somogyi-Nelson method for glucose determinations was used at intervals of 3, 6, 9, 12 and 24 hours, and 2, 4, 6, 10, 14, 30, 45 and 60 days. The average blood sugar values initially for the lean animals was about 132 mg/100 ml; after 6 hours the level had fallen to about 59 mg/100 ml, reaching a minimum level of 50 mg/100 ml at 9 hours. Within 24 hours the blood sugar levels were back to normal levels comparable to those of controls. The initial level of nearly 300 mg/100 ml in obese animals had nearly doubled within 12 hours, peaking at about 600 mg/100 ml in 4 days. Sixty days later, the blood sugar levels in the obese mice were still about double the initial values.

Glucose tolerance tests after intraperitoneal injection of 50 mg glucose per animal following caffeine injection 10 days earlier in a group of 15 obese mice, compared with the results in 10 nontreated (no caffeine) obese mice, showed little effect on blood sugar levels among the treated animals; the nontreated group showed a characteristic increase in blood sugar levels. AT the time of the glucose tolerance tests, the treated animals showed levels of about 400-600 mg/100 ml; the untreated blood sugar levels were about half that. The failure of the treated animals to show appreciable increase was probably due to the already-high glucose levels; any increase in blood glucose resulted in rapid appearance in the urine. Urinalyses confirmed this explanation.

Insulin tolerance tests conducted 15 days after fasting (24 hours) and unfasting, treated (caffeine) and untreated animals with a simple unit of crystalline insulin showed no increased sensitivity to insulin among obese mice due to caffeine treatment. Histologic studies of caffeine-treated and nontreated obese hyperglycemic mice showed no observable cause for the hyperglycemic effect of caffeine.

Solutions of coffee and sugar containing 0.33 mg caffeine/ml were given orally ad libitum with a regular diet to 30 obese and 20 lean mice for 7 days. The average weekly intake of the coffee solution was 30-50 ml. After 7 days, the animals were returned to water in the diet. Blood glucose determinations were made at intervals from 3-100 days after the testing period. The blood sugar levels of the lean animals were unaffected by the coffee intake; blood glucose levels among the obese mice rose gradually during the 7-day coffee intake, and even though the animals were given 3 days after caffeine before testing the "late effect of coffee intake, the glucose levels continued to rise steadily, peaking at 7 days after coffee intake had ceased. Sixty-eight days after coffee had been withdrawn, the obese animals still showed elevated blood sugar levels. On the 90th day, however, the blood sugar levels had fallen to very low levels, less than half the initial pretreatment levels. By the 100th day 18 of the 24 mice had died. The possible relevance of this unexpected action of caffeine to the management of maternity-onset diabetes in obese human subjects warrants further study, the authors suggest - particularly in view of the large consumption of coffee.

Khanna and Cornish (1665) in 1973 reported on the effect of daily ingestion of caffeine on the microsomal enzymes of rat liver. Male Sprague-Dawley rats weighing 250-300 g were given caffeine in the drinking water; the daily dose amounted to 20-24 mg/kg. Three different experiments were

conducted. Liver samples were taken from the anesthetized animals at the conclusion of each test and prepared for enzyme and other analyses, which included N-demethylation studies, hydroxylation activities, and cytochromes P_{450} and b_5 values.

In the first experiment, 5 groups of rats, each with 6 treated and 2 control animals, were variously sacrificed at 4, 8, 14, 28 and 56 days after the start of caffeine administration. The results are shown in the following table:

Table 1 shows the effect of daily caffeine ingestion (20–24 mg/kg) on the mixed-function drug-metabolizing microsomal enzymes of the livers of rats killed at intervals of 4-56 days

Table 1. *Hepatic microsomal-enzyme activity in rats given 20–24 mg caffeine/kg/day in the drinking-water*

Duration of dosing (days)	Acetanilide hydroxylation (% of control)*	Aminopyrine *N*-demethylation (% of control)*
4	123 ± 4	115 ± 7
8	127 ± 12	104 ± 11
14	145 ± 11	90 ± 6
28	139 ± 7	73 ± 3
56	93 ± 9	38 ± 5

*Values are means for six treated rats at each sacrifice period ±SEM. Two control rats were killed at each time.

The second study consisted of a 6-week caffeine administration, on the last 3 days of which 25 mg/kg/day sodium phenobarbitone were intravenously injected into some treated and control animals. The results indicated that caffeine-treated animals were not able to respond to the phenobarbitone treatment to the same degree as those not pretreated with caffeine. The following table shows the results:

Table 2. *Effect of phenobarbitone on the hepatic microsomal enzymes of rats given 20–24 mg caffeine/kg/day in the drinking-water for 6 wk*

Treatment	No. of animals/group	Acetanilide hydroxylation (% of control)*	Aminopyrine *N*-demethylation (% of control)*
None	3	100 ± 8	100 ± 5
Caffeine	6	110 ± 12	80 ± 11
Phenobarbitone†	5	200 ± 13	186 ± 19
Phenobarbitone† + caffeine	6	157 ± 12	140 ± 9

*Values are means for the numbers of animals shown ±SEM.
†Phenobarbitone (25 mg/kg) was injected ip on each of the last 3 days of the caffeine treatment.

In the third study, the caffeine treatment lasted for 14 weeks, during the last 3 days of which phenobarbitone, 25 mg/kg/day were injected. The hepatic microsomal levels of cytochrome P_{450} and cytochrome b_5 were determined: the following table shows the results:

Table 3. *Effect of phenobarbitone administration on cytochrome P_{450} and b_5 levels of hepatic microsomes of rats given 20-24 mg caffeine/kg/day for 14 wk*

Treatment	No. of animals/group	Cytochrome P_{450} (nmoles/mg protein)*	Cytochrome b_5 (nmoles/mg protein)*
None	4	1·10 ± 0·09	1·09 ± 0·04
Caffeine	6	1·13 ± 0·05	0·98 ± 0·06
Caffeine + phenobarbitone†	6	1·60 ± 0·11	0·74 ± 0·05

*Values are means for the numbers of animals shown ±SEM.
†Phenobarbitone (25 mg/kg) was injected ip on each of the last 3 days of caffeine treatment. The animals were sacrificed 24 hr after the last dose.

Using 17 150-day-old male hooded rats, Zimbardo and Barry (3585) in 1958 examined the sexual behavior of male rats following the i.p. injection of caffeine. A dose of 20 mg of caffeine was observed to enhance the sexual activity of the rats; that is, they showed an increased frequency of mounting, copulation and ejaculation compared to control animals receiving injections of isotonic saline.

As detailed in the following table, for 13-28 days Heppel et al. (1377) in 1947 fed various levels of caffeine to male weanling Sprague-Dawley rats maintained on a low casein-high fat diet deficient in choline. Analysis of the rats' livers for total chloroform-soluble substances at the end of the feeding periods indicated that caffeine possesses lipotropic activity.

TABLE I

Influence of Caffeine, Theobromine and Theophylline on Liver Fat Content of Rats Fed Choline-Deficient Diet

Group	No. of rats	Dietary treatment	Initial body weight (average)	Final body weight (average)	Liver weight (average)	Liver fat content (average)
		Experiment 1				
			g.	*g.*	*g.*	*per cent*
I	10	Basal diet for 21 days	46.5±1.4*	45.5±1.7	4.12±0.22	28.4±1.5
II	8	Basal diet for 27 days	45.6±1.1	46.3±2.0	4.02±0.28	29.8±2.9
III	13	0.3% Caffeine for 21 days	48.1±1.6	39.6±1.8	2.24±0.09	11.9±1.1
IV	11	0.3% Caffeine for 27 days	49.9±1.7	40.4±1.5	2.66±0.16	17.3±1.8
V	7	0.3% Caffeine for 13 days, then 0.4% caffeine for 8 days.	45.9±2.2	36.1±2.0	2.04±0.09	9.5±1.0
VI	5	0.3% Caffeine for 13 days, then 0.4% caffeine for 8 days, then 0.6% caffeine for 7 days.	46.0±1.7	34.6±1.7	2.16±0.13	13.5±2.3

* Including the standard error of the mean calculated as $\sqrt{d^2/N-1}/\sqrt{N}$.

Naismith et al. (2299) in 1969 fed a starch-based diet (which contained no cholesterol) supplemented with freeze-dried tea, decaffeinated coffee, coffee, or pure caffeine to male, 120 g Sprague-Dawley rats for 54 days. As the caffeine dosage increased from 4.8 to 140.0 mg caffeine per 100 g diet, the plasma cholesterol and phospholipid levels increased and the triglycerides decreased. (See table 3). The pyruvate kinase activity (an index of lipogenesis) in the livers of rats fed coffee plus the basic diet was not altered. Other studies have found that coffee raised cholesterol, phospholipid, and triglyceride levels when added to diets containing cholesterol. Tea caused these parameters to decrease. The authors concluded that the presence or absence of cholesterol in the diet affects the changes in plasma lipids due to coffee or tea. In the present study, both tea and coffee decreased triglyceride levels. Since this parameter may be more important than cholesterol or lipid levels in the development of atherosclerosis and heart disease, tea and coffee drinking in humans are not considered to be causative factors by the authors.

TABLE 3

Median values for plasma lipids of control rats, and rats fed tea, decaffeinated coffee, coffee or caffeine for 54 days (nine rats per group)

Dietary supplement	Caffeine added per 100 g diet	Total cholesterol	Phospholipids	Triglycerides
	mg/ml	*mg/100 ml*	*mg/100 ml*	*mg/100 ml*
None	Control	85 (75–105) [1]	137 (124–149)	38 (23–65)
Sanka	4.8	85 (55–115)	143 (102–206)	34 (18–44)
Tea	77.9	95 (70–120)	159 (121–174)	29 (17–52)
Coffee	136.2	105 (80–130)	171 (126–191)	30 (19–42)
Caffeine	140.0	105 (90–140)	174 (131–190)	27 (20–41)

[1] Figures in parentheses give range of values.

Statistical analyses (*P* values)

Control versus Sanka	ns [2]	ns	ns
Control versus tea	ns	0.025	0.01
Control versus coffee	0.025	0.01	ns
Control versus caffeine	< 0.005	< 0.005	0.01
Coffee versus Sanka	0.005	0.05	ns

[2] ns = not significant.

Heyden et al. (1399) reported in 1969 a study of the effects of caffeine on blood cholesterol and atherogenesis in rabbits. Three groups of male, white New Zealand rabbits weighing 1.5-2 kg were used in the experiments: Group A received an atherogenic diet which included 1 g cholesterol/day plus 50 mg instant coffee per day; Group B received the same diet without coffee but were given daily subcutaneous doses of 0.22 ml caffeine benzoate (25 mg caffeine); and Group C received only the atherogenic diet without additional treatment, serving as the control group. The experiment lasted for 84 days. Blood samples were taken for cholesterol determinations, and after sacrifice of the animals at the end of the experiment, hearts and aortas were removed and examined for arterial and coronary atherosclerotic lesions.

Within a few weeks of treatment, the cholesterol levels rose in the rabbits in all three groups, but statistically significant difference among the groups was not observed. No relationship between coffee consumption and the development of ischemic heart disease was demonstrated. The doses used in this experiment (12.5-16.7 mg) are comparable to a daily human intake equivalent to 9-12 cups of coffee averaging 100 mg caffeine per cup. The authors suggest that, even though animal experimental results "cannot be directly applied to the process of atherogenesis and the development of both hypercholesterolemia and clinical ischemic heart disease in man", they would "hesitate to accept without confirmation a single epidemiological observation showing a positive relation between coffee intake and coronary disease".

In an effort to determine the effect of caffeine upon gastric sec-

retion, Roth and Ivy (2718) in 1944 administered 250 mg doses of caffeine to dogs subcutaneously, intramuscularly and intravenously. In no instance did this treatment stimulate gastric secretion. In cats, however, 65-125 mg doses of caffeine administered i.v. or through a pyloric cannula provoked a marked stimulation of gastric secretion. Stimulation of gastric secretion was also observed in human subjects following administration of 250 mg of caffeine by i.m. injection or by stomach tube.

By the use of x-ray examinations, Foti and Egyed (991) in 1953 found that s.c., i.v. and oral administration of caffeine (0.01-0.05 g/kg) in the dog cause increased gastric evacuation, animated peristalsis in the upper small intestine decreasing toward the colon, and some colonic spasticity. These effects were found to be dose-dependent and to vary with the mode of dosage parenteral administration being the most effective.

The stimulatory action of caffeine on the central nervous system was demonstrated by Scott and Chen (2900) in 1944 by several methods. The injection of caffeine into the tail veins of starved albino mice was observed to produce convulsions, which were mainly tetanic in nature. A value of 84.4 mg/kg was determined to be the mean convulsive dose. The oral administration of 200 mg of caffeine to adult human subjects was found to increase both critical fusion frequency of flicker and finger-tapping rate. Augmentation of respiration in dogs deeply anesthetized with sodium phenobarbital was produced.

The diuretic effect of caffeine was tested by the authors in dogs by intravenous injection of 10 mg/kg and in human subjects by oral administration of 200 mg. These doses resulted in increased urine output in both dogs and man.

Bellet et al. (227) in 1968 administered 25 mg/kg caffeine sodium benzoate, i.v., to 22 dogs, 8 to 14 kg in weight. A control group of 11 dogs was given no treatment. Blood clotting parameters and free fatty acid levels were determined on blood samples collected for 4 hours after the caffeine treatment. Both the heparin tolerance time and the recalcification time were significantly shortened 210 to 270 minutes after the caffeine was given. In this same time period, the prothrombin time was 0.66 plus or minus 0.12 seconds less than that of the controls, which was shortened by 0.29 plus or minus 0.08 seconds. The authors felt that this was a significant decrease, since the normal prothrombin time in dogs is 7.5 seconds. The concentration of serum free fatty acids was significantly elevated as early as 90 minutes after the caffeine was given. Parameters which were unchanged by caffeine were the Stypven time, the partial thromboplastin time, the clotting time in glass tubes, and the clotting time of diluted and undiluted blood in silicone tubes. The authors believed that the increased FFA levels due to caffeine were responsible for the decreased coagulation times.

Several cytological studies of the effects on HeLa cell division in vitro of continuous exposure to caffeine at levels comparable to or exceeding the maximum concentrations in human blood (about 5 microgram/ml) after ingestion of 8 cups of coffee, were reported in 1971 by Thayer et al. (3218). Both continuous flow culture of HeLa cells in suspension, and propagation and subculture of adherent HeLa cells were continuously exposed to levels of 5-20 micrograms/ml of caffeine and examined for chromosomal aberrations, particularly chromatid breaks.

The results of a typical experiment using the suspension technique is shown in the following table:

TABLE I

EFFECT OF CAFFEINE ON GROWTH AND CHROMATID BREAKAGE OF HeLa CELLS IN CONTINUOUS CULTURE (Chemostat Expt. 1)

Duration of exposure (days)	*Control*			*Caffeine (5 μg/ml)*		
	Cell count per ml (× 10⁵)	*Cell divisions (cum.)*	*Chromatid breaks*[a]	*Cell count per ml (× 10⁵)*	*Cell divisions (cum.)*	*Chromatid breaks*
0	6.3		0	5.0		
1	6.2	0.9	0.04	4.6	1.5	0
2	5.2	3.0	0	4.9	2.8	[b]
3	5.2	4.7	0	5.2	4.3	0.04
4	5.0	6.2	0.04	5.3	5.4	0
5	5.0	7.6	0	6.2	6.3	0
6	5.0	9.2	0.08	5.0	7.3	0.08
7	↓ 4.9[c]	10.5	0	5.0	8.2	0
8	↑ 6.2	10.8	0	4.8	9.4	0.04
9	5.2	12.1	0	4.7	10.4	0
10				4.8	12.0	[b]
11				4.6	12.8	0.04

[a] Breaks calculated per cell; 25 mitoses examined daily.
[b] Sample lost.
[c] ↑, flow on; ↓, flow off.

Adherent cultures produced results as shown in the following table:

TABLE IV

EFFECT OF CAFFEINE ON GROWTH AND CHROMATID BREAKAGE OF HeLa CELLS IN CONTINUOUS CULTURE

Continuous culture for 9 weeks, subcultured twice weekly.

Weeks	*Control*		*Concentration of caffeine*					
			5 μg/ml		*10 μg/ml*		*20 μg/ml*	
	Cum. divisions	*Chromatid breaks*	*Cum. divisions*	*Chromatid breaks*	*Cum. divisions*	*Chromatid breaks*	*Cum. divisions*	*Chromatid breaks*
1	5.2	—	4.6	—	5.2	—	4.8	—
2	9.7	—	9.0	—	9.7	—	7.4	—
3	13.4	—	12.1	—	12.5	—	10.4	—
4	18.9	1, 0	16.4	1, 0	16.4	1, [illegible]	15.4	2, 1
5	24.9	2, 1	22.2	1, 0	22.3	2, 2	21.6	2, 2
6	31.0	0, 2	28.4	0, 0	28.5	0, 1	24.9	1, 0
7	36.6	0, 2	33.1	2, 2	34.2	1, 0	28.4	0, 0
8	41.7	2, 0	38.9	0, 1	40.2	1, 1	32.6	0, 0
9	47.8	0, 0	45.7	0, 2	46.5	0, 0	39.3	1, 0
Total breaks		10		9		10		9
Breaks/cell[a]		0.028		0.025		0.028		0.025

30 mitoses examined per sample, 2 samples per week.

[a] 30 mitoses × 12 observations = 360 mitoses examined per caffeine level.

—, cells not spreadable; changed to EAGLE's medium after 3 weeks.

In neither type of experimental technique employed was there any significant increase in the incidence of chromatid breaks due to exposure to caffeine. Growth was not significantly affected in either situation at the levels of caffeine employed.

The effects of coffee ingestion on oral glucose tolerance curves in normal human subjects was reported by Feinberg et al. (934) in 1968. Twenty-three normal healthy adults were placed on a diet containing at least 300 g carbohydrate 3 days prior to the initial study, and were fasted after 10 pm of the night preceding the test. On each of two mornings, 1 g glucose/kg body weight was given orally to each subject; on one of the two mornings, 5 g instant coffee (220 mg caffeine) was given along with the glucose. Blood samples were taken prior to and at 30, 60, 90, 120 and 180 minutes after the test meal; blood glucose concentrations, and in some instances serum free fatty acids, were determined. Serum immunoreactive insulin was also determined. The caffeine effects on glucose tolerance tests are shown in the following table, only the 30 and 60 minute periods show a significant effect:

Table 1.—*Effects of Coffee Ingestion on Oral Glucose Tolerance Curves in Humans*

Minutes After Ingestion of Test Meal	Number of Subjects	Blood Glucose Concentration of Control Subjects (mg. %)	Blood Glucose Concentration of Subjects Ingesting Coffee with Test Meal (mg. %)	Mean Difference	Variance	Standard Error of the Mean	t	P
0	23	80.3 ± 9.0*	79.2 ± 10.9*	1.1				N.S.†
30	18	139.1 ± 25.4	117.7 ± 18.6	21.2	694.30	6.21	3.41	<0.01
60	23	121.7 ± 24.3	98.6 ± 24.0	23.2	615.06	5.17	4.48	<0.001
90	15	90.1 ± 25.7	83.0 ± 12.8	7.1				N.S.
120	23	77.1 ± 21.7	72.6 ± 30.3	4.5				N.S.
180	23	68.2 ± 14.1	72.8 ± 12.3	4.6				N.S.

*Mean ± S.D.

†Differences not statistically significant at the 5 percent level for a paired comparison.

No difference was observed in control and test group serum free fatty acid concentrations until 3 hours after the test meal; at that time, the group receiving coffee showed a significant increase in free fatty acid concentration. The immunoreactive insulin values were not significantly different in test and control groups. The following tables summarize the data:

Table 2.—*Effects of Coffee Ingestion on Serum Free Fatty Acid Levels During Course of Glucose Tolerance Test*

Minutes after Ingestion of Test Meal	Number of Subjects	FFA Concentration of Control Subjects (% of zero time sample)	FFA Concentration of Coffee Ingesting Subjects (% of zero time sample)	Mean Difference	Variance	Standard Error of the Mean	t	P
30	13	84.5 ± 18.0*	82.8 ± 18.5*	−1.7				N.S.†
60	18	75.7 ± 24.3	81.1 ± 24.8	5.4				N.S.
90	11	67.8 ± 20.3	67.9 ± 15.4	0.1				N.S.
120	18	73.3 ± 27.5	82.7 ± 23.5	9.4				N.S.
180	15	86.5 ± 33.3	117.6 ± 36.8	20.9	1281	9.565	2.196	<0.05

*Mean ± S.D.

†Differences not statistically significant at the 5 percent level for a paired comparison.

Table 3.—*Effects of Coffee Ingestion on Serum Immunoreactive Insulin Levels During Course of Glucose Tolerance Test*

Minutes after Ingestion of Test Meal	Number of Subjects	Immunoreactive Insulin Levels of Control Subjects (μU/ml.)	Immunoreactive Insulin Levels of Subjects Ingesting Coffee with Test Meal (μU/ml.)	Mean Difference	P
0	23	15.3 ± 11.2*	13.2 ± 13.4*	2.1	N.S.†
30	17	83.2 ± 56.0	95.6 ± 45.9	12.4	N.S.
60	23	93.9 ± 60.1	85.5 ± 45.1	8.4	N.S.
90	17	64.5 ± 40.8	63.0 ± 42.8	1.5	N.S.
120	22	33.9 ± 24.3	28.1 ± 24.0	5.8	N.S.
180	22	13.0 ± 14.5	13.8 ± 18.4	0.8	N.S.

*Mean ± S.D.

†Differences are not statistically significant at the percent level for a paired comparison.

Bellet et al. (224) in 1965 studied the effects of caffeine in the form of coffee and as the sodium benzoate on human subjects with regards to the free fatty acid serum concentrations. Normal male subjects, ages 18 to 63 were studied; 12 subjects received instant coffee containing 218 mg caffeine; 11 subjects were given 500 mg caffeine sodium benzoate intramuscularly; and 11 controls were injected with 500 mg sodium benzoate in buffered saline. In the first group, given the equivalent of two and a half cups of coffee, the subjects served as their own controls by ingesting 500 ml water with a sweetner.

The free fatty acid concentrations were determined from blood samples taken before and at 30, 60, 90, 120 and 180 minutes after dosing. The results are shown in the following tables:

Table 1.—*Free Fatty Acid Concentrations After Coffee and After Water in the Same Subject*

		Serum Free Fatty Acids (μEq/liter)					
		Time (Minutes)					
Subject	Beverage	0	30	60	90	120	180
1	Coffee	340	339	392	623	723	790
	Water	406	330	376	368	294	341
2	Coffee	817	670	989	830	1232	1283
	Water	795	700	866	647	669	962
3	Coffee	736	518	600	670	969	1042
	Water	516	372	342	300	284	318
4	Coffee	387	419	406	374	339	516
	Water	502	514	458	563	790	609
5	Coffee	213	168	135	180	174	341
	Water	189	110	163	182	218	130
6	Coffee	536	529	750	964	854	1010
	Water	714	390	672	624	706	774
7	Coffee	266	357	340	554	617	744
	Water	564	582	258	306	366	300
8	Coffee	868	525	525	550	575	918
	Water	582	499	535	450	451	630
9	Coffee	825	581	931	712	812	932
	Water	324	318	257	214	183	189
10	Coffee	1068	1500	1156	1300	2462	2537
	Water	941	866	995	736	766	946
11	Coffee	249	402	644	714	881	884
	Water	164	—	394	477	541	647
12	Coffee	789	535	777	712	702	812
	Water	324	456	300	288	294	288

TABLE 2.—*Free Fatty Acid Concentrations After Intramuscular Injections of Caffeine Sodium Benzoate and Sodium Benzoate*

Caffeine Sodium Benzoate						Sodium Benzoate					
Serum Free Fatty Acids (μEq/Liter)						Serum Free Fatty Acids (μEq/liter)					
	Time (Minutes)						Time (Minutes)				
Subject	0	30	90	120	180	Subject	0	30	90	120	180
13	260	340	377	349	374	24	325	335	255	344	293
14	335	307	505	545	535	25	251	267	202	182	162
15	323	336	305	388	417	26	326	328	306	341	331
16	590	515	755	690	740	27	545	590	615	585	535
17	458	491	481	745	665	28	1045	1205	1145	1300	1326
18	384	570	645	675	1015	29	497	319	232	400	287
19	505	675	500	550	730	30	333	—	307	334	398
20	625	571	680	596	705	31	523	538	549	673	629
21	625	655	765	810	860	32	300	326	300	331	375
22	675	670	750	785	840	33	425	431	367	390	475
23	203	225	246	265	249	34	437	408	274	392	344

A consistent and significant effect of ingested coffee and injected caffeine on free fatty acid mobilization is shown by the data. The mechanism by which caffeine produces the marked increase in the serum free fatty acid levels is not clearly understood by the authors, who do, however, refer to a reported positive association between coffee intake and coronary heart disease.

A later paper (1968) by Bellet, Keishbaum and Finck (226) supplements the human studies described above by an animal study, using 26 mongrel dogs of both sexes, weighing 7 to 18 kg. Half the animals (13) were injected intramuscularly with caffeine sodium benzoate, 25 mg/kg caffeine, and half served as controls. Pre-injection blood samples were taken, as were post-injection samples, and the free fatty acid concentrations determined. The results are shown in the following figure which demonstrates the significant increase in the mean serum free fatty acid due to caffeine:

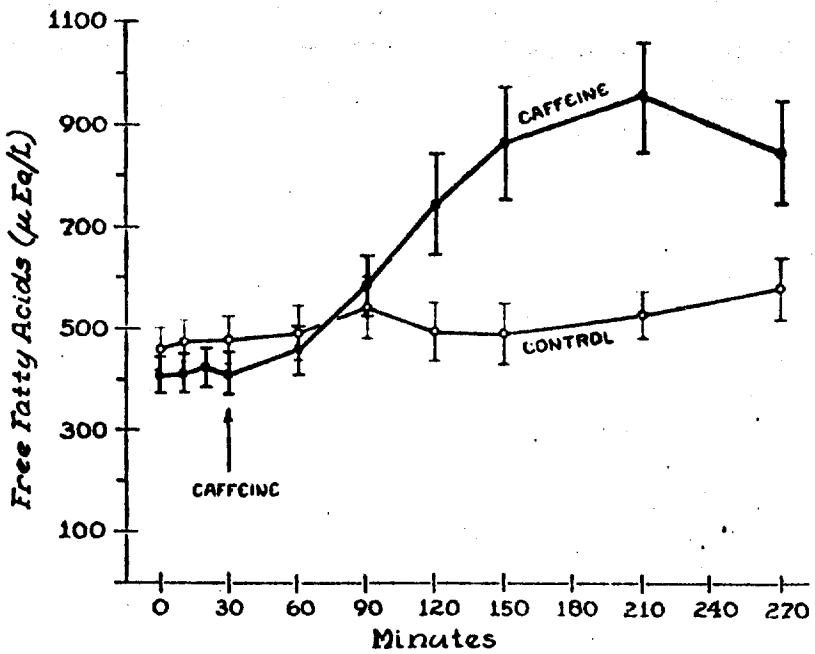


Fig. 1.—Plasma FFA concentrations in 13 anesthetized dogs after caffeine sodium benzoate (25 mg./Kg.) administered intravenously. Note that rise begins within 30 minutes after its administration. Peak is attained at about 3 hours; then FFA concentration gradually decreases.

The effects of cola drinks on the free fatty acid (FFA) metabolism in human subjects was studied by Bellet et al. (225) in three different experiments. Healthy male subjects, aged 14 to 42 years were given 16 oz. regular cola (with sugar); some amount of diet cola (sugar-free); or 16oz. carbonated water. Blood samples were taken before and 1, 2, 3 and 4 hours after ingestion of the beverage, and plasma FFA concentrations were determined. Estimates of the caffeine content in various colas were: regular cola, 5 to 7 mg/oz.; sugar-free cola, 3.2 to 3.8 mg/oz. Those colas used in the present studies had 109 mg caffeine in regular cola and 46 mg caffeine in the diet cola/16 oz. bottle.

After ingestion of regular cola, the mean FFA concentration decreased during the first two hours, but then increased to a maximum at four hours; the initial value was 598 microequivalents/liter, the final concentration rose by 155 plus or minus 61 microequivalents/liter. The mean FFA concentration after the diet cola rose steadily to a maximal level at 4 hours, 48% above the initial value. No appreciable change was observed after the control carbonated water.

The initial drop in FFA concentration after the regular, sugar-containing cola was probably due to the suppression of caffeine-induced FFA mobilization by the sucrose through reesterification of the released FFA, according to the authors.

A brief report of a case history by Alberti et al. (45) in 1972

of a patient with diabetes mellitus is included here because of a prolonged treatment (18 months ?) with caffeine in doses of up to 7 g/day, equivalent to 50 cups of instant coffee. Tests made before and six days after withdrawal of the caffeine showed no change in glucose tolerance and only minimal changes in insulin secretion. A moderate decline in plasma free fatty acids and a marked full in circulating ketone bodies were the major changes noted.

The effects of coffee-consumption on the sympatho-adrenomedullary function in man as reflected in the urinary excretion of adrenaline and noradrenaline were reported in 1967 by Levi (1928). Eight men and one woman, healthy medical students, were placed on a strict regime of diet, tobacco and all drugs forbidden, and were given 300 ml coffee containing 75 mg/100 ml caffeine (a 225 mg dose). Urine samples were collected and analyzed fluorimetrically for adrenaline and noradrenaline. Eight control subjects were similarly treated except that no coffee was served.

For several hours preceding and following the 2-hour "coffee period" urinalyses were also performed: the results for both adrenaline and noradrenaline compared with controls are shown in the following figures:

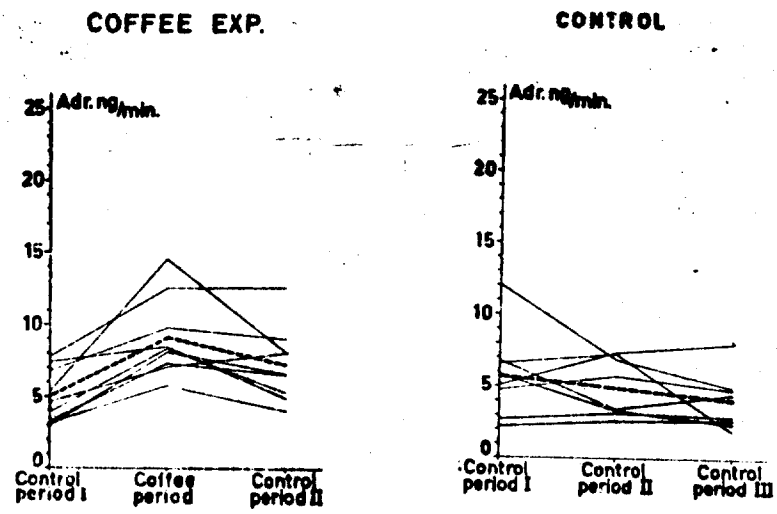


Fig. 1. Urinary excretion of adrenaline (ADR) during the coffee experiment (left) and under control conditions (right). Short-dash line indicates mean values.

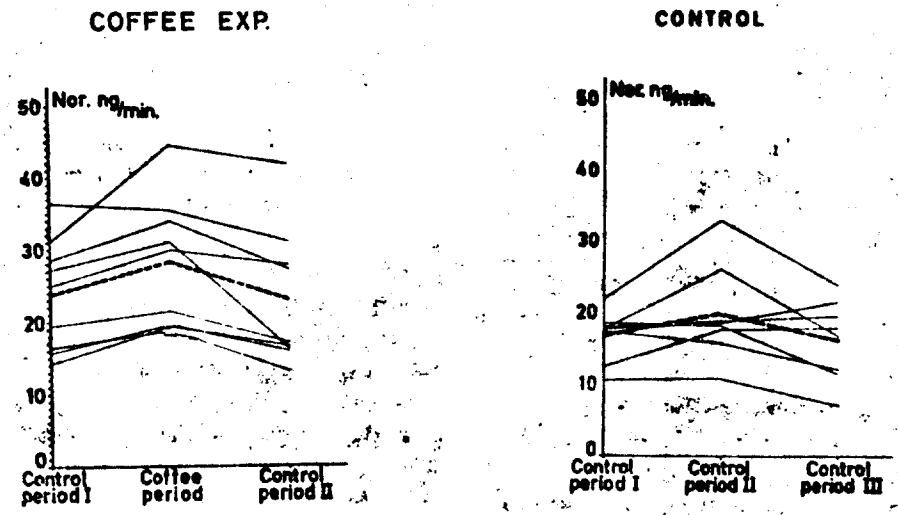


Fig. 2. Urinary excretion of noradrenaline (NOR) during the coffee experiment (left) and under control conditions (right). Short-dash line indicates mean values.

The increase due to the caffeine in urinary adrenaline excretion was significant, less so in noradrenaline excretion. Urine volume, specific gravity and creatinine excretion remained substantially unchanged.

Avogaro et al. (130) in 1973 investigated the influence of age on caffeine effects in plasma and urine cortisol levels in human subjects. Thirty normal subjects, 21 males and females; of ages ranging from 15 to 70 years accustomed to drinking at least 2 cups of coffee daily, were fasted for 12 hours and given instant coffee containing 250 mg caffeine. At other times the subjects served as their own controls, ingesting only water; at least 5 days were allowed to elapse between coffee and water tests. During the four hours of testing, eating, drinking and smoking were not permitted; the patients were kept in bed during this period. Periodic blood samples were taken, an ECG tracing was monitored, and urine was collected during the 4 hours of testing. Blood glucose, plasma free fatty acid, glycerol, cortisol and creatinine were determined; urinary volume excreted, creatinine and cortisol contents were determined.

Blood glucose levels showed no appreciable change after coffee ingestion. Significant increases in other constituents, plasma and urinary (except volume and creatinine clearance) were observed; the following table summarizes the data:

TABLE 2. *Maximal variations in plasma FFA, and glycerol, plasma and urinary cortisol, urinary volume and creatinine clearance after ingestion of coffee*

Measured parameter	*Subjects*			
	All subjects	*Group I (15 to 40 years)*	*Group II (41 to 55 years)*	*Group III (56 to 70 years)*
FFA, μEq/liter				
Coffee	+74.3 ± 22.9	+96.1 ± 21.2	+63.7 ± 18.0	+63.0 ± 10.9
Water	+5.4 ± 4.0	+7.6 ± 4.3	+4.8 ± 3.9	+3.7 ± 3.7
P	< 0.001	< 0.001	< 0.001	< 0.001
Glycerol, μmoles/liter				
Coffee	+51.4 ± 12.9	+57.7 ± 16.7	+47.1 ± 12.6	+49.5 ± 5.4
Water	+4.9 ± 3.4	+4.3 ± 3.3	+5.3 ± 4.2	+5.0 ± 4.6
P	< 0.001	< 0.001	< 0.001	< 0.001
Plasma cortisol, μg/100 ml				
Coffee	+55.4 ± 20.7	+67.6 ± 23.6	+50.5 ± 21.7	+48.2 ± 10.0
Water	−24.7 ± 11.2	−26.2 ± 9.1	−25.0 ± 7.3	−22.7 ± 16.1
P	< 0.001	< 0.001	< 0.001	< 0.001
Urinary cortisol, μg[a]				
Coffee	109 ± 24	115 ± 29	100 ± 26	113 ± 14
Water	83 ± 24	79 ± 25	80 ± 29	90 ± 21
P	< 0.01	< 0.01	< 0.01	< 0.01
Urinary volume, ml[a]				
Coffee	686 ± 344	964 ± 323	572 ± 236	522 ± 301
Water	634 ± 318	823 ± 247	491 ± 173	589 ± 413
P	> 0.05	> 0.05	> 0.05	> 0.05
Creatinine clearance, ml				
Coffee	114 ± 46	127 ± 57	112 ± 49	103 ± 27
Water	108 ± 39	129 ± 53	100 ± 28	94 ± 26
P	> 0.05	> 0.05	> 0.05	> 0.05

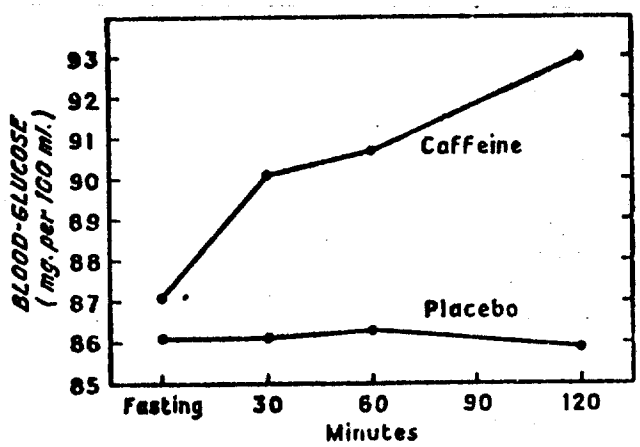
[a] Excreted during the 240 min of the test.
The variations are expressed as percent of the basal values and given as means ± SD. The urinary cortisol and creatinine output and urinary volume are referred to in absolute values.
A comparison between the data obtained in the three groups shows a significant difference ($P < 0.01$) for FFA, (both matching groups I and II, and I and III) and for cortisol (between I and II, and I and III). All other differences are not significant.

When the data were considered according to age groups, a greater increase in plasma free fatty acid and cortisol levels was shown in the younger subjects than in the older. No other age-dependent differences were found.

The authors discuss the possibility of atherogenic properties of coffee due to the increase in plasma free fatty acid (see Bellet et al. in this section of monograph), but note that in normal people, coffee seems to represent a transient supply of additional substrate in the synthesis of plasma lipids, especially when carbohydrates are not available. The greater reaction among the younger patients to coffee suggests a greater sensitivity of the suprarenal gland, and "in older people the lipid-mobilizing effect of coffee and its possible consequences seem to be of lesser importance.

Deakins (709) observed in 1939, from four glucose-tolerance tests performed on himself at different times with caffeine and coffee, that large doses of caffeine (0.5 g) depress the peak of the human sugar-tolerance curve and slightly delay the return of blood-glucose to baseline values. In further tests he found that caffeine alone does not raise the blood sugar appreciably.

The blood-glucose levels of 22 presumably healthy junior dental students following oral ingestion of 250 mg of caffeine were observed by Cheraskin et al. (568) in 1967, to be significantly higher than the blood-glucose levels of 21 students ingesting a placebo (see following figure).



Effect of caffeine-versus-placebo supplementation on blood-glucose studied during a two-hour period.

In an experiment by Bellet et al. (228) in 1969, 13 normal, young male subjects, aged 18-22 years, were given, orally, 5 g of instant coffee (220 mg caffeine) dissolved in 500 ml of water following an overnight fast. Analysis of the urine collected during the next 3 hours revealed a significant increase in the urinary excretion of 11-hydroxycorticosteroid (11-OHCS), indicating a stimulation of the adrenocortical activity. The fact that caffeine stimulates adrenocortical secretion was given further support by experiments on dogs, in which a significant increase in the plasma 11-OHCS level was found in the phrenico-abdominal vein within one hour after i.v. administration of caffeine (50 mg caffeine sodium benzoate/ kg body weight.

Bachmann et al. (140) in 1942, conducted a series of experiments on the induction of creatinuria in man by the oral administration of caffeine. As shown in the following table, they found that the minimal dose capable of inducing creatinuria is 1.0 mg/kg. There was no apparent relationship between the amount of caffeine ingested and the amount of creatine excreted. Likewise, there was no correlation between the amount of creatine in the urine and the total O_2 consumption or CO_2 elimination; nor was there any relationship between the occurrence of creatinuria and the gaseous exchange. The presence of creatine in the urine was not related to an increase in carbohydrate oxidation, but was associated with an increase in protein metabolism.

TABLE 1

Urinary excretion of creatine after ingestion of various amounts of caffeine

CAFFEINE INGESTED PER KILO BODY WEIGHT	NUMBER OF EXPERIMENTS	NUMBER OF EXPERIMENTS WITH CREATINE IN THE URINE IN P-E PERIOD	RANGE	HOURLY EXCRETION OF CREATINE (AVG. OF ALL EXPTS.)	HOURLY EXCRETION OF CREATINE (AVG. OF EXPTS. IN WHICH CREATINE WAS EXCRETED)
mgm.			*mgm.*	*mgm.*	*mgm.*
None*	10	0		0	0
0.6	8	0		0	0
1.0	14	3	0.9-1.4	0.4	1.2
1.8	6	4	0.6-1.5	0.7	1.0
3.0	12	11	0.8-4.7	1.6	1.7
3.6	7	7	1.5-4.2	2.2	2.2
6.0	10	8	0.7-2.2	1.0	1.4

* Control experiments.

Clark and De Lorimier (598) in 1926, studied the effect of caffeine ingestion on uric acid excretion in healthy human males. They were given either a high protein and purine diet or a low-purine diet for a control period of 7 days, then oral doses of caffeine ranging from 250 to 1000 mg per day were added to the basic diet, and finally another control period of 3 to 11 days. Blood and urine samples were obtained at various intervals

during the experimental periods. The ingestion of caffeine increased the amount of uric acid in both the blood and the urine, but this effect was not dose-related. The initial increase in uric acid excretion within 8 to 12 hours was followed by a decrease. An apparent depression of active excretion was observed after prolonged caffeine administration.

The effect of various types of coffee on fat metabolism in 41 healthy subjects and in 44 patients with liver diseases was studied by Zeller (3572) in 1968. Blood samples were taken both before the coffee was given and 30, 60, 120, 180, 240, and 360 minutes after. The subjects were fasted for 12 hours prior to the coffee administration. Twenty g of coffee in 250 ml was given orally and contained one of the following caffeine levels - 9 mg (decaffeinated coffee), 193 mg (steamed coffee), 201 mg (coffee pretreated with CO_2), or 225 mg (Columbia coffee). The decaffeinated coffee produced no change in FFA in the plasma of healthy or diseased subjects. All of the caffeinated coffees produced an increase in serum FFA in a dose-related way. The increase in FFA was greater and longer-lasting in the patients with liver diseases than in the healthy subjects. Zeller explained that this was because the normal liver can take up about 50% of the FFA from the deposited fat by enzymatic splitting of triglycerides. Therefore, the diseased liver would not be able to metabolize the excess fats to the extent that the healthy livers could.

Ruffo (2744) in 1972 discussed in some detail the relationship between caffeine and intermediary metabolism, particularly with regard to phosphorylase and concentrations of cyclic AMP. The introduction of caffeine into the reactions involving AMP results in a competitive inhibition of the specific phospho-diesterase that hydrolyzes cyclic AMP; thus caffeine may participate in the regulatory mechanism of a fundamental enzyme, influencing the metabolic sequence of primary physiological importance such as glycogenolysis. An increased AMP also activates the lipase responsible for the free fatty acids. The details of Ruffo's proposed model for the pharmacological mechanism of drugs on enzyme systems would explain the hyperglycemia, the lipolytic effect, the increase of lactic acid in the muscle, and the increased O_2 consumption which follow the administration of caffeine in higher animals.

Wachman et al. (3417) in 1970 instructed 8 healthy humans, 4 males and 4 females aged 20 to 42, to abstain from caffeine or other methylxanthine-containing foods for 1 week. The subjects were then fasted overnight and, in the morning, given 10 g decaffeinated instant coffee (Sanka) in 250 ml distilled water, 100 degrees C, orally in 10 minutes. A blood sample was drawn immediately after the coffee ingestion. Then, 0.5 g/kg glucose in 100 ml saline was injected i.v. in 2 to 4 minutes, after which blood samples were obtained every 10 minutes for 1 hour. After 2 to 5 days, the test was repeated in the same subjects, only using 10 g of nondecaffeinated coffee (Maxwell House). The caffeine content of the Sanka was 65 mg and that of the Maxwell House was 449 mg. In contrast to the ingestion of decaffeinated coffee, nondecaffeinated coffee elevated the fasting blood

glucose levels, exerted a hyperglycemic effect as shown by impaired glucose tolerance tests, and reduced the insulin response to glucose injection.

The effect of caffeine on the reflex activity of the spinal cord in dogs was reported in 1960 by Danilov (688). Three dose-levels of caffeine, administered "internally" (orally ?) were employed: 3.5-8 mg/kg; 20-35 mg/kg; and 40-80 mg/kg. After 30 minutes, three different experiments were conducted, each consisting of many tests in each category. The effect of caffeine on the patellar reflex and its inhibition used 5 intact dogs, 6 dogs with complete spinal cord transection and 3 sympathectomized spinal dogs. In the majority of instances with intact and spinal dogs, the patellar reflex was reduced and its inhibition increased; phasic changes were observed in the sympathectomized animals.

A second series of tests were carried out to determine the caffeine-effect on the chronaxie of the flexor reflex; the same conditions as above were generally observed (intact, spinal and sympathectomized). With small doses of caffeine, a reduction of chronaxie was seen; with larger doses, phasic changes were characteristic, with a reduction in chronaxie during the first day, and an increase thereafter. Parallel to the chronaxie experiments a third test of the caffeine influence on crossed extensor reflex was performed. The thresholds were lowered for 4 days after larger doses of caffeine, and for 1-2 days at the low doses; phasic changes in some of the animals were observed.

In general, the experiments showed that caffeine produced profound shifts in the reflex activity of the spinal cord; the intensity and duration of the caffeine effect on the spinal cord were dose-dependent, and direct.

The increase in serum free fatty acids following administration of caffeine reported by a number of investigators lead Strubelt et al. (3116) in 1970 to study the possibility of an hepatotoxic effect of caffeine (and theophyllin). Male Wistar rats, weighing 280-360 g were kept in groups of 5 animals each and were fed a standard diet ad libitum. Caffeine and theophyllin were given intraperitoneally or subcutaneously in concentrations of 1% in 0.9% saline solution. Sixty milligrams per kilogram of the drug given once, or at repeated intervals of 24 hours by either route produced an increase in the free fatty acids of 137 to 149% of control values. (The animals were sacrificed, blood drained and livers removed and examined histologically at 2 hours after the last dose of caffeine or theophylline). Concentrations of free fatty acids, esterified fatty acids, cholesterine, glutamate-oxalacetate-transaminase and glutamate-pyruvate transaminase in the serum were determined. The results are shown in the following table:

Nr.	A Behandlung	B Dosis/kg (ip.)	T (h)	N	FFS (µval/l)	VFS (mval/l)	Cholesterin (mg/100 ml)	SGOT (mU/ml)	SGPT (mU/ml)	C Fettgehalt der Leber (mg/g)
1	a Coffein	60 mg	2	8	433 ± 15*)	6,7 ± 0,9	113 ± 16	75,1 ± 6,6*)	18,4 ± 1,5*)	41 ± 1,4
	0,9%NaCl	6 ml	2	8	183 ± 36	5,5 ± 0,4	130 ± 26	58,4 ± 3,9	14,6 ± 0,9	39 ± 0,7
2	Coffein	60 mg	16	9	172 ± 13	4,5 ± 0,6*)	78 ± 17	114,0 ± 31,0	18,2 ± 2,0	41 ± 1,5
	0,9%NaCl	6 ml	16	7	144 ± 17	7,5 ± 1,0	97 ± 10	67,4 ± 6,0	15,1 ± 4,3	41 ± 3,1
3	Coffein	60 mg[1)]	2	12	282 ± 36*)	5,1 ± 0,2	108 ± 16	57,9 ± 4,0	15,0 ± 0,8	39 ± 1,0
	0,9%NaCl	6 ml[1)]	2	8	151 ± 22	5,8 ± 0,4	137 ± 20	53,9 ± 2,3	14,1 ± 0,7	37 ± 0,8
4	Coffein	60 mg[2)]	2	10	479 ± 14*)	7,3 ± 0,7	181 ± 11	58,1 ± 5,6	16,0 ± 1,0	40 ± 2,7
	0,9%NaCl	6 ml[2)]	2	10	230 ± 28	5,9 ± 0,4	186 ± 9	53,8 ± 1,4	13,1 ± 1,0	40 ± 1,3
5	Theophyllin	60 mg	2	11	542 ± 69*)	6,0 ± 0,5	138 ± 14	65,5 ± 2,8*)	12,6 ± 1,7	40 ± 1,5
	0,9%NaCl	6 ml	2	10	218 ± 19	5,3 ± 0,2	124 ± 1	53,7 ± 3,5	15,7 ± 1,2	53 ± 4,0
6	Theophyllin	60 mg[1)]	2	12	418 ± 52*)	4,9 ± 0,6	92 ± 16	53,0 ± 5,4	13,3 ± 1,2	44 ± 2,2
	0,9%NaCl	6 ml[1)]	2	11	178 ± 14	5,8 ± 0,7	119 ± 19	55,7 ± 2,7	14,3 ± 1,1	41 ± 2,0
7	Coffein	100 mg	2	10	450 ± 45*)	6,4 ± 0,6	266 ± 8	54,0 ± 5,7	10,6 ± 1,0	44 ± 1,0
	Theophyllin	100 mg	2	10	359 ± 37*)	6,9 ± 0,3	252 ± 8	62,6 ± 2,8	11,4 ± 0,9	44 ± 2,0
	0,9%NaCl	10 ml	2	10	153 ± 22	7,3 ± 0,5	260 ± 5	59,1 ± 2,9	10,5 ± 0,8	44 ± 1,0
8	Coffein	100 mg	16	10	412 ± 79*)	5,1 ± 0,6	234 ± 10*)	62,4 ± 7,8	13,9 ± 1,9	47 ± 3,0*)
	Theophyllin	100 mg	16	10	345 ± 37*)	6,2 ± 0,5	223 ± 12	59,7 ± 4,5	9,0 ± 0,9	47 ± 2,4*)
	0,9%NaCl	10 ml	16	10	209 ± 31	6,3 ± 0,5	179 ± 20	58,7 ± 3,3	11,6 ± 0,7	38 ± 1,0

1) Diese Tiere erhielten die gleiche Behandlung auch an den 3 vorausgehenden Tagen.
2) Bei dieser Versuchsgruppe erfolgte die Injektion subcutan.

Key:
A. treatment B. dose/kg C. fat content of the liver
a. caffeine
1) These animals received the same treatment on the 3 preceding days as well.
2) Injection to this test group was subcutaneous.

Histological examination of the liver showed no aberrant results attributable to caffeine (or theophylline); the authors "found no definite evidence of a hepatotoxic activity of the methylxanthines".

Ammon and Estler (77) in 1973 studied the influence of age on the effects of caffeine on the heart function and metabolism in Sprague Dawley rats. Two age-groups of rats were studied: those just reaching puberty or 2 month-old rats; and 15-18 months old animals. Each age group was divided into two groups and anesthetized, one receiving 40 mg/kg caffeine intravenously, and a control group given an equal amount of 0.9% NaCl. Blood pressure was measured before and for 30 minutes after dosing; cardiac frequency was also recorded. At 30 minutes after dosing, the thorax was opened and the heart quick-frozen, removed, and treated for the determination of pyruvate and lactate; adenosinetriphosphate and creatinphosphates were also determined.

An increased heartbeat frequency was observed in both young and old rats ten minutes after treatment with caffeine, but the frequency dropped within 20 minutes to normal in young animals and remained high in old rats for the full 30 minutes duration of the experiment. Blood pressure in-

creased slightly and temporarily in young rats but the increase in the older animals was more marked and of longer duration. The lactate/pyruvate ratio (l/p) increased to a greater degree in the older rats presumable due to the greater increase in cardiac activity. No difference in age-groups was observed in the phosphates content of the heart; both decreased to the same degree.

V. Drug Interaction

The popular notion that a person who has over-indulged in alcoholic beverages to the point of "stumbling drunkedness" can be "sobered up" by gulping great quantities of coffee has long been a theme of novel and movie. In view of the generalization that alcohol is a central depressant and caffeine a central stimulant, the forestated popular notion would appear reasonable. Hughes and Forney (1473) in 1961 performed experiments with various alcohol-caffeine combinations on the behavior of rats. Weaning male rats were trained in special shock-avoidance box described in the following figure:

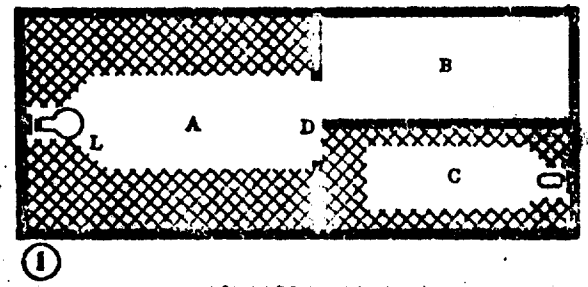


FIG. 1. Apparatus and training method. A, main compartment: warning light, shocking grid floor. B, safe escape area: not illuminated, insulated floor. C, unsafe escape area: illuminated, shocking grid floor. D, Guillotine-type door. L, warning light.

Only those animals that had learned to respond with 100% accuracy to the "anxiety-producing"warning light by an escape to the safe area were used in the experiment. This simple, conditioned avoidance response, was initiated by a warning light, followed in 5 seconds by an electric shock applied to the metal 2nd floor of the main compartment. An animal leaving this compartment only after the shock is recorded as one with unconditioned avoidance response. The rat must make the decision to escape into one of two compartments, the first of which is similar to the main one, and the second is darkened and safe from shock. It is the animal who after several days of training invariably escapes to the safe compartment upon the stimulus of the warning light that is used in the alcohol-caffeine treatments. The drugs were administered intraperitoneally; alcohol as a 5% solution, the caffeine as the citrate salt in dose levels of 50, 100 or 150 mg/kg. After the drugs were injected, the animals were tested 3 times every 15 minutes for 4 hours and were then discarded. Ninety rats in all were tested. Ethanol, 1 g/kg; caffeine, 50, 100 and 150 mg/kg; and combinations of 1 g/kg ethanol plus each of the three caffeine levels were tested. Control rats received only saline.

Alcohol alone caused a slight (5%) reduction of the conditioned response during the first hour of testing; the small dose (50 mg/kg) of

caffeine alone caused no significant reduction in response. The intermediate caffeine dose (100 mg/kg) produced a moderate reduction in conditioned responses for only the first 2 hours of testing. The largest caffeine dose (150 mg/kg) caused a marked reduction in response lasting longer than the 4-hour testing period. When the 1 g/kg ethanol was combined with caffeine, the reduction in conditioned response was greater than could be explained by a summing of individual drug responses. The potentiation was most evident in the intermediate caffeine dose (100 mg/kg) plus the ethanol; no drug antagonism was observed.

In this study it was shown that the dose of 1 g/kg ethanol had largely disappeared from the blood within 2 hours; caffeine at 100 mg/kg produced altered behavior (hyperexcitability) in some animals during the first 2 hours, with behavior then returning to normal. The combined drugs produced gross depression in the animals, apparently correlated with the reduction in conditioned avoidance response. Alcohol evidently altered behavior in a manner such that recovery was not complete, even when no alcohol remained in the blood stream; the evidence indicated that recovery had scarcely begun when zero blood levels of alcohol had been reached.

Scriabine and Bellet (2906) in 1967 tested the presumption, based on studies from the 1930's and from pharmacology tests, that caffeine reduces digitalis toxicity. Mongrel dogs, 6-14 kg body weight were used in the experiments; the drugs were caffeine as the caffeine sodium benzoate and digitalis as digoxin. The animals were anesthetized, respiration maintained artificially, femoral artery and vein cannulated, and blood pressure recorded. Digoxin was infused as an ethanol-saline solution containing the theoretical lethal dose of digoxin (0.25 mg/kg) per 90 ml solution. Caffeine sodium benzoate, 50 mg/kg was given intramuscularly 1 hour prior to anethesia and digoxin infusion, or where given by infusion with the digoxin, as a dose of 72-110 mg/kg. The infusion rate was constant at 1 ml/min. For 30 minutes after infusion began the blood pressure was recorded at 5 minute intervals and continuously thereafter. Each experiment was terminated when blood pressure fell abruptly and electrocardiographic evidence indicated ventricular fibrillation. Seven control experiments showed an LD_{50} for digoxin of 0.26 mg/kg; eight dogs pretreated with 50 mg/kg caffeine intramuscularly and then given digoxin showed an LD_{50} of 0.27 mg/kg. The standard errors were plus or minus 0.02 for digoxin alone, and 0.01 for pretreated caffeine. Seven animals infused with digoxin and caffeine sodium benzoate simultaneously gave LD_{50} values of 0.23 plus or minus 0.01 mg/kg; this is not significantly different (at 95% level) from the control LD_{50}. An additional experiment in which the caffeine was given at 25 mg/kg or intravenously at 100 mg/kg, 5 minutes prior to the digoxin infusion, did not show significant results differing from the lethal dose range of digoxin in controls.

The results of these experiments did not substantiate reported antagonism of digitalis toxicity by caffeine.

Newman and Newman (2346) undertook a study in 1956 to test dexedrine

and caffeine in ordinary therapeutic dosages as practical antagonists to alcohol. Six subjects from staff and student body of a medical school were used in the experiments. A choice of alcoholic beverages was provided; the dose of alcohol amounted to 0.1 ml alcohol per pound of body weight (about 180 mg/kg, or total dose of about 12-13 g ethanol), diluted to 20% concentration with plain or carbonated water, and was consumed within 5 minutes and repeated at 20 minute intervals.

The drugs, dexedrine or caffeine, were ingested 45 minutes before the start of the experiment; the dose of dexedrine was 15 mg, of caffeine, 300 mg. Four tests of the nervous system function were used to assess the depressant effect of alcohol as influenced by dexedrine or caffeine: an equilibrium test, balancing on one foot with eyes closed; hand steadiness by holding at arm's length a small metal stylus within a slightly larger hole without touching edge of hole; electroencephalographic stable rhythm records; and fusion-flicker frequency measurements. The results of the tests are shown in the following table:

TABLE 1.—*Blood Alcohol Concentration at which Failure on Tests Occurred with Alcohol Alone, Alcohol and 15 mg. of Dexedrine, and Alcohol and 300 mg. of Caffeine.**

Subject	*Medication*	*Balance*	*Steadiness*	*Fusion*	*EEG*
He.	Alcohol	152	138	24	170
	Alc. + Dexed.	150	168	40	95
	Alc. + Caff.	165	121	18	115
Sc.	Alcohol	90	55	P110	75
	Alc. + Dexed.	85	62	P110	70
	Alc. + Caff.	102	68	P104	48
Ca.	Alcohol	95	80	30	63
	Alc. + Dexed.	110	P121	P121	57
	Alc. + Caff.	105	83	P123	70
Co.	Alcohol	110	110	38	100
	Alc. + Dexed.	120	118	P126	123
	Alc. + Caff.	122	132	P135	92
Po.	Alcohol	73	68	P85	P85
	Alc. + Dexed.	65	55	P72	58
Ed.	Alcohol	151	92	P151	122
	Alc. + Dexed.	155	95	P163	90

* P indicates that the test was passed at the maximum blood alcohol concentration attained. The maximum concentration is shown following the letter.

Neither dexedrine nor caffeine was demonstrated to be an effective antagonist to the depressant effect of alcohol when used at ordinary therapeutic dosages.

A study demonstrating that caffeine stimulates during metabolism in rats was presented by Mitoma et al. (2207) in 1969. Male Sprague-Dawley rats were used in the experiments; the weight of the animals varied from 160 to 300 g with one exception. Phenobarbital was used throughout the study as a reference compound. The animals were pretreated for 3 days with

caffeine and phenobarbital. After sacrifice, the livers were removed and variously treated (for details refer to paper in documents section of monograph), yielding samples of hepatic microsomes, as the site of the drug-metabolizing activity of the liver. The effects of phenobarbital and of caffeine given separately are summarized in the following table which is self-explanatory:

TABLE III

EFFECT OF PHENOBARBITAL AND CAFFEINE ON RAT LIVER MICROSOMES

Treatment[a]	Final body weight (g)	Liver weight (g/100 g)	Microsomal protein (mg/g of liver)	CO-binding pigment[b] (mμmole/mg of protein)	Acetanilide hydroxylase (μmoles/g protein)	p-Chloro-N-methylaniline N-demethylase (μmoles/g protein)
Saline (0.2 ml), ip, twice daily	222 ± 15	4.64 ± 0.25	16.80 ± 0.86	0.341 ± 0.114	11.9 ± 1.9	44.9 ± 2.5
Phenobarbital (38 mg/kg), ip, twice daily	246 ± 17 $p < .05$	5.52 ± 0.36 $p < .001$	21.74 ± 2.37 $p < .001$	0.912 ± 0.113 $p < .001$	27.7 ± 2.7 $p < .001$	61.4 ± 3.6 $p < .001$
Saline (0.5 ml), oral, twice daily	221 ± 5	4.52 ± 0.18	17.48 ± 2.24	0.427 ± 0.145	9.0 ± 2.1	33.5 ± 3.8
Caffeine (75 mg/kg), oral, twice daily	225 ± 24	4.56 ± 0.17	17.25 ± 2.52	0.570 ± 0.270	24.5 ± 5.3 $p < .001$	46.4 ± 6.2 $p < .005$

[a] Six rats (200 g) in each group were treated as indicated for 4½ days. The interval between the last dose and sacrifice was 4 hr for caffeine-treated rats and 5 hr for phenobarbital-treated rats. The results are expressed as the mean ± SD

[b] Based on molar extinction of 91 cm^{-1} mM^{-1} at 450 mμ (11).

This study contains many details which must be omitted here. One of some interest, however, is summarized in the following table which shows the effects of phenobarbital and caffeine, given both separately and simultaneously, upon the microsomal hepatic drug-metabolizing activities. The two drugs were additive in effects as stimulants only when acetanilide was the substrate.

TABLE VI

EFFECT ON THE HEPATIC DRUG-METABOLIZING ACTIVITIES OF CAFFEINE AND PHENOBARBITAL ADMINISTERED SEPARATELY AND SIMULTANEOUSLY[a]

Group	Product formed (μmoles/g protein ± SD)		
	Acetanilide	o-Nitroanisole	Aminopyrine
Saline	5.4 ± 2.1	11.4 ± 1.4	5.0 ± 2.0
Caffeine	15.4 ± 1.0	16.1 ± 3.1	9.9 ± 1.4
	$p < .001$	$p < .05$	$p < .01$
Phenobarbital	14.8 ± 2.2	20.9 ± 2.1	25.6 ± 3.6
	$p < .001$	$p < .001$	$p < .001$
Caffeine + phenobarbital	23.1 ± 1.5[b]	22.9 ± 2.4	26.7 ± 1.2
	$p < .001$	$p < .001$	$p < .001$

[a] Four rats (170 g) were used per group. The rats were injected ip with saline, caffeine (75 mg/kg, twice daily), phenobarbital (38 mg/kg, twice daily) or with a mixture of caffeine and phenobarbital (twice daily) for 3 days.

[b] Significantly different from caffeine or phenobarbital values at $p < .001$.

The authors suggest that the stimulating action of caffeine was due to a stimulation of "de novo" synthesis of hepatic microsomal enzymes, yet without causing a net increased synthesis of the enzymes.

The foregoing paper by Mitoma, et al. was preceded by a study by Mitoma, Sorich and Neubauer (2206) in 1968 in which the authors presented data from rat experimentation indicating that caffeine acts as an inducer of the liver microsomal system. Doses of caffeine given orally to rats were 100, 75 or 50 mg/kg daily for 3 days; within 4 hours of the last dose, the animals were sacrificed and livers removed and prepared for assay of the drug metabolizing activities. In all cases the microsomal activities with respect to acetanilide, o-nitroanisole, and aminopyrine metabolism were higher in the caffeine-treated groups than in controls.

The minimum caffeine intake showing microsomal interaction was 40 mg/kg which is equivalent to about 35 cups of coffee a day for a 70-kg man on a straight weight basis, or to about 8 cups daily on the basis of metabolic weight (body weight to the three-fourths power). The authors speculate that it is not unlikely that moderate intake of coffee by man may have an inducing effect on the liver drug-metabolizing system.

Epstein et al. (884) in 1970, did several studies administering caffeine in combination with known mutagens to see if caffeine potentiated their effects in male, 8-10 week old Swiss mice, strain ICR/Ha. Caffeine was

administered either once i.p. at 168 to 200 mg/kg doses or orally in the drinking water at a dose level of 0.05 to 0.4% (4 mg to 32 mg/day, assuming the mice consumed 8 ml/day, which equals 200-1600 mg/kg/day using 0.02 kg for the mouse weight) for 8 weeks. The mutagens used in combination with caffein were methylmethanesulfonate (50 mg/kg), TEPA (0.312-1.25 mg/kg), and x-rays (50-250 r). The treated mice were mated with untreated, virgin females for 8 weeks afterward. The females were then autopsied in 13 days and the numbers of early and late fetal deaths and live and dead uterine implants were determined. Caffeine was not found to synergize the 3 mutagens used, by increasing early fetal deaths or pre-implantation losses. The only significant result was that caffeine apparently reduced the rate of pregnancies in the early weeks of mating, after a single injected dose of caffeine in combination with x-rays. This effect was similar to that when caffein was given alone.

Haldi et al. (1287) in 1947, found that the simultaneous administration of 1500 mg/kg sucrose, with 75 mg/kg caffeine in aqueous solution by stomach tube reduced the spontaneous increase in activity in the rat caused by caffeine. Sucrose given 30 minutes after caffeine also reduced the effect of caffeine. The same reduction in the effect of caffeine was observed with 10000 mg/kg peptone or using 3.75 ml vegetable oil as the vehicle for 20 mg caffeine. Agar (10%) had no effect on the stimulation of caffeine, when used as the vehicle.

VI. Consumer Exposure Information

It is not unlikely that caffeine is the most-consumed drug of all; the universal beverages - coffee, tea, cocoa and cola "soft-drinks" are consumed in great quantities. Caffeine is available in tablet form to keep you awake, or to "eat a cup of coffee". It is used medically as a central nervous system, respiratory and cardiac stimulant in doses of 200 mg, orally (The Merck Index), or by injection, subcutaneously, intramuscularly or intravenously in doses of 200-500 mg, as the sodium benzoate of caffeine. Side-effects of caffeine include - nervousness, insomnia and tachycardia.

Efforts to associate caffeine ingestion, chiefly as coffee or tea, with the etiology of heart disease have to this time proven inconclusive.

The following tables were compiled from data submitted by user firms. Food consumption values for each food category were derived from the Market Research Corporation of America (MRCA) data on the frequency of eating, and from the USDA data on mean portion size of foods in each category. The food consumption values thus derived were coupled with the usage level data obtained in the surveys to calculate the daily intake of the substance.

Table 2 reports the usage of caffeine in foods; table 11 reports the annual poundage data. Table 13 reports the possible daily intake and total dietary, based on food consumption by total sample. Table 14 indicates the potential daily intakes by age category.

TABLE 2 -- USAGE LEVELS REPORTED FOR NAS APPENDIX A SUBSTANCES (GROUP I) USED IN REGULAR FOODS(R)

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO.	NAME	# FIRMS REPORTING	*** USUAL USE *** WTD MEAN, %	*** MAXIMUM USE *** WTD MEAN, %
CAFFEINE NAS 0034 FEMA 2224	01	BAKED GOODS(R)	*	.00561	.00680
	07	FROZN DAIRY(R)	*	.03000	.04000
	16	SOFT CANDY(R)	*	.03000	.04000
	20	GELATIN PUD(R)	*	.03000	.04000
	23	BEV TYPE I(R)	29	.01295	.01413

TABLE 11, PART A -- ANNUAL POUNDAGE DATA FOR NAS APPENDIX A SUBSTANCES (GROUPS I & II)

SUBSTANCE NAME (SURVEY NO.)	# REPORTS TO NAS 1960/1970	POUNDAGE REPORTED TO NAS (MATCHING REPORTS FOR BOTH YEARS) 1960	1970	TOTAL 1970 POUNDAGE REPORTED TO NAS	# REPORTS TO FEMA	POUNDAGE REPORTED TO FEMA-- 1970 ONLY	TOTAL 1970 POUNDAGE NAS + FEMA
CAFFEINE NAS 0034 FEMA 2224	*/ *	721,667	737,467	737,467	26	653,075	1,390,542

TABLE 13, PART A -- POSSIBLE DAILY INTAKES OF NAS APPENDIX A SUBSTANCES (GROUPS I & II), PER FOOD CATEGORY AND TOTAL DIETARY, BASED ON FOOD CONSUMPTION BY TOTAL SAMPLE - - - SEE EXPLANATORY NOTES IN EXHIBITS SECTION

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO.	NAME	# OF FIRMS	(AGE)	POSSIBLE DAILY INTAKE, MG. AVERAGE	HIGH A	HIGH B
CAFFEINE NAS 0034	01	BAKED GOODS(R)	*	0-5 MO.	.190740	.252450	.231200
				6-11 MO.	1.424940	2.905980	1.727200
				12-23 MO.	3.057450	5.037780	3.706000
				2-65+ YR.	7.696920	11.433180	9.329600
CAFFEINE NAS 0034	07	FROZN DAIRY(R)	*	0-5 MO.	.300000	1.230000	.400000
				6-11 MO.	2.850000	7.920000	3.800000
				12-23 MO.	4.320000	10.140000	5.760000
				2-65+ YR.	7.680000	18.510000	10.240000
CAFFEINE NAS 0034	16	SOFT CANDY(R)	*	0-5 MO.	.060000	.600000	.080000
				6-11 MO.	.660000	2.040000	.880000
				12-23 MO.	1.050000	2.790000	1.400000
				2-65+ YR.	1.740000	5.280000	2.320000
CAFFEINE NAS 0034	20	GELATIN PUD(R)	*	0-5 MO.	.600000	.810000	.800000
				6-11 MO.	3.840000	11.640000	5.120000
				12-23 MO.	4.140000	10.080000	5.520000
				2-65+ YR.	6.120000	15.750000	8.160000
CAFFEINE NAS 0034	23	BEV TYPE I(R)	29	0-5 MO.	.310800	.466200	.339120
				6-11 MO.	2.935650	10.062150	3.207510
				12-23 MO.	7.018900	21.043750	7.658460
				2-65+ YR.	13.468000	35.962150	14.695200
CAFFEINE NAS 0034	ALL CATEGORIES		30	0-5 MO.	1.461540	3.358650	1.850320
	**********			6-11 MO.	11.714590	34.568130	14.734710
	**********			12-23 MO.	19.586350	49.091530	24.044460
	**********			2-65+ YR.	36.704520	86.935330	44.744800

TABLE 14, PART A -- POTENTIAL DAILY INTAKES OF NAS APPENDIX A SUBSTANCES (GROUP I & II), PER FOOD CATEGORY, BASED ON FOOD CONSUMPTION BY EATERS ONLY - - - SEE EXPLANATORY NOTES IN EXHIBITS SECTION

FOOD CATEGORY	SUBSTANCE NAME NO.	NAME	(SURVEY NO.) AGE)	NO. OF FIRMS	POTENTIAL DAILY INTAKE, MG., PER CATEGORY AVERAGE	HIGH A	HIGH B	(VERY HIGH
	CAFFEINE NAS 0034	FEMA 2224		*	7.050000	0-5 MO.	21.660000	9.400000	28.880000
					6.870000	6-11 MO.	14.340000	9.160000	19.120000
					6.090000	12-23 MO.	12.480000	9.040000	16.600000
					9.270000	2-65+ YR.	18.780000	12.360000	25.040000

CAFFEINE

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